VOLUME 60 • AUGUST 1958 • NUMBER 2

AMA ARCHIVES OF OPHTHALMOLOGY

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Bertha Klien

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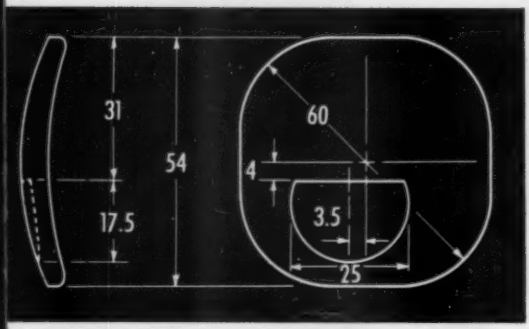

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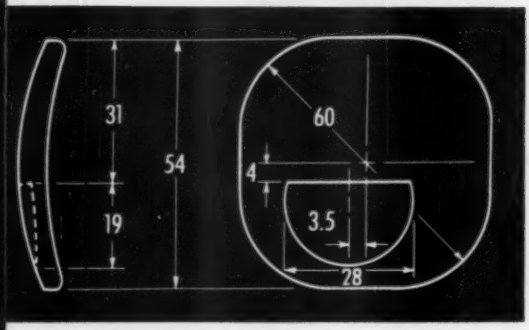

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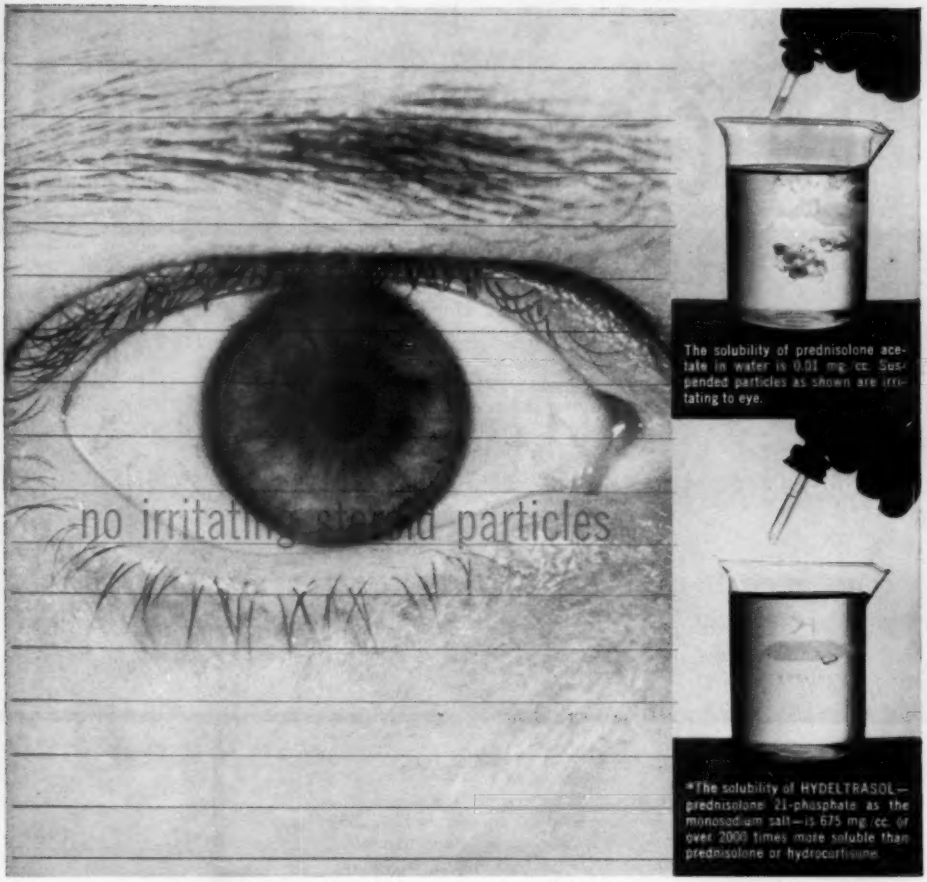
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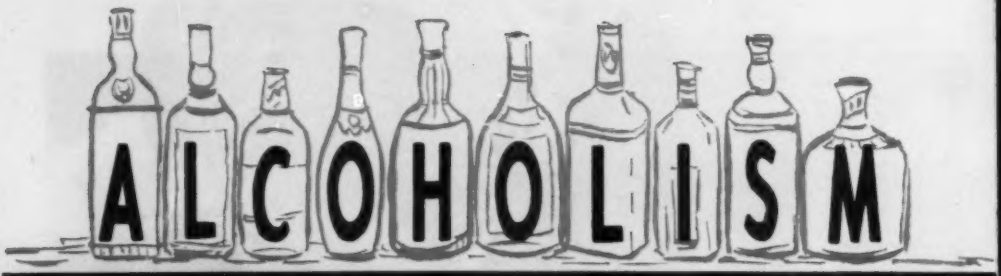

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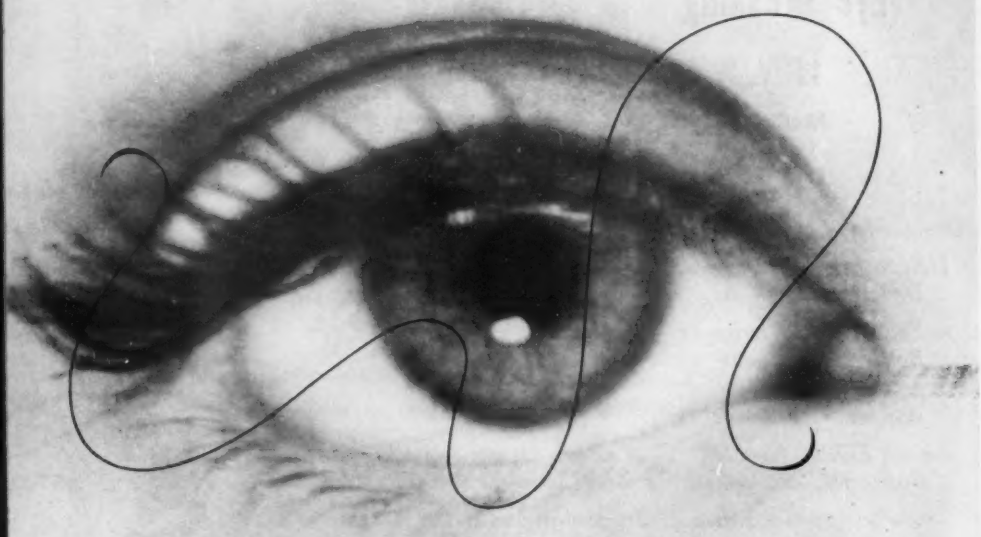

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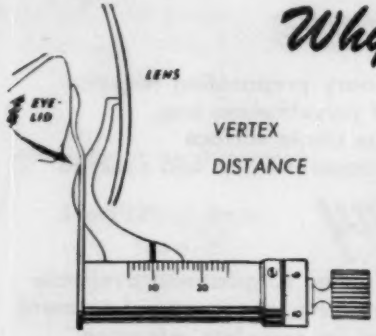

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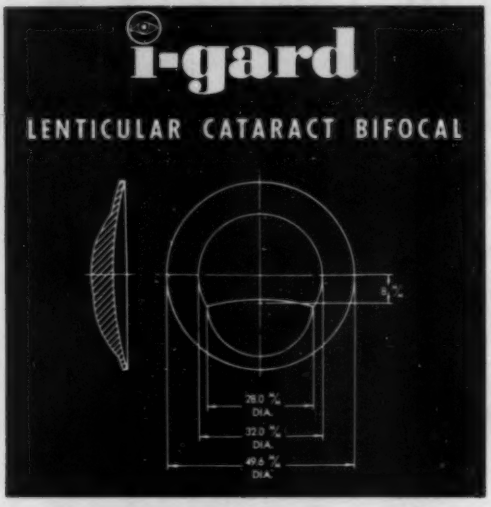

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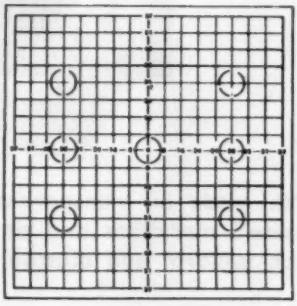

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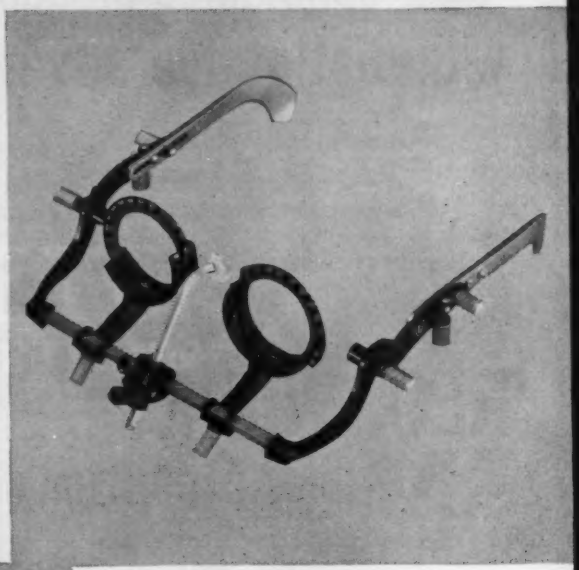

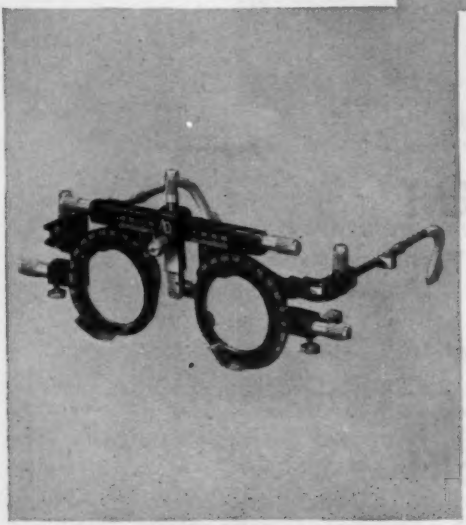

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Diseases of the Macula

Basic Histopathologic Processes in Retina, Pigment Epithelium, and Choroid Which Modify Their Clinical Appearance

BERTHA KLIEN, M.D., Chicago

The pluripotential responses of retina, pigment epithelium, and choroid to a variety of pathogens produce a fascinating multiplicity of lesions which modify, often characteristically, the clinical picture of macular disease.

The Retina

1. Opacities of the Macular Retina.—Any foreign matter deposited within the retinal layers, as a result of either infiltrative, exudative, or proliferative processes, changes its index of refraction and becomes clinically visible as an opacity in the otherwise almost transparent structure. Unless caused by hemorrhage or pigment invasion the opacity is light in color. Three of the four types of whitish opacities occur frequently in the macular region.

1. Lipoid Deposits: Clinically the individual lesion is small, discrete, and of brilliant pure white or yellowish-white color, depending upon the intensity of illumination. There is a tendency for grouping and confluence into arborescent or circinate patterns. They arise in areas of chronic relative anoxia, and in and around hemorrhages and stagnant retinal edema.

Histologically these deposits consist of large and small cavities filled with fatty granular cells. In the retina, as throughout the central nervous system, these scavenger cells are supplied mainly by the microglia (Hortega cells) in response to a demand for phagocytes. Other sources of retinal phagocytes are the cells of Mueller and the pigment epithelium.

These accumulations of fatty granular cells appear most striking in sections stained with Sudan III, but they may be recognized also in sections processed in the ordinary manner. In the latter they appear as large vesicular cells whose nuclei have disintegrated or become pyknotic and whose colorless cytoplasm contained the lipid material before it was extracted in the processing and which may still show a slightly foamy pattern.

Their occurrence is very common in circulatory disturbances of all types and in the subacute phase of inflammatory processes, but they are rare in degenerative lesions unless they are accompanied by hemorrhagic episodes. They are consistently absent in malignant melanoma, and so their presence aids in ruling out a tumor.

2. Inspissated Exudates: Colloid-like residua of extravasations other than hemorrhage appear clinically as irregularly shaped yellowish or grayish-white patches of greatly varying size and varying sharpness of outline. The histologic picture shows cavities filled with a homogeneous, massive-appearing coagulum.

In diabetic retinopathy of long duration, some forms of circinate retinopathy, and

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Fig. 1 (Case 1).—L. E., man, aged 63, circinate retinopathy. L. vision, 20/200; same fundus as in Figure 3, four years later.

other conditions, one occasionally encounters large, unusually white, inert masses which do not change their appearance for many months or even years (Fig. 1). Histologically they consist of a mixture of inspissated exudates and fatty granular cells (Fig. 2), the latter producing the strikingly white color.

An unusual clinical picture may arise through diffuse coating of an elevated subretinal macular lesion by fatty granular cells. Again, the abundantly present lipid material aids in differentiating the condition from malignant melanoma. Such observations were made in the following case.

CASE 1.—A man, aged 59, had noted failing left vision for seven months prior to his first examination, at which time the left vision was 20/100. The other eye was normal.

There were an elevated dark-gray lesion just temporal to and below the left fovea and slight edema of the overlying retina which extended into the foveal region.

During the following two months a deep retinal hemorrhage at the border of the elevated lesion and a white coating over its surface appeared (Fig. 3), which suggested a macular disease of vascular origin rather than a choroidal melanoma.

It is interesting that during the following four years of observation this eye developed typical circinate retinopathy (Fig. 1) and that during the fifth year sudden complete loss of left vision occurred as a result of occlusion of the left central retinal artery, all these successive events pointing to a severe disease of the retinal arterial tree.

The histologic picture of the macular lesion in another eye with circinate retinopathy (Fig. 4) shows such a coating of its anterior surface with fatty granular cells.

3. Glial Scars: Destruction of retinal tissue is repaired in a manner similar to that of brain tissue, namely, by proliferation of neuroglia (Fig. 5). The resulting ophthalmoscopically visible opacity is a somewhat ill-defined, yellowish, flat, and lusterless patch. Extensive macular lesions of this type may be found after recovery from venous occlusions. More frequently they are

Fig. 2 (Case 2).—L. E., man, aged 55, death due to diabetic nephropathy. Circinate retinopathy, large fatty granular cells mixed with exudate corresponding to circinate lesion. Colloidal iron-Van Gieson stain; ×155.

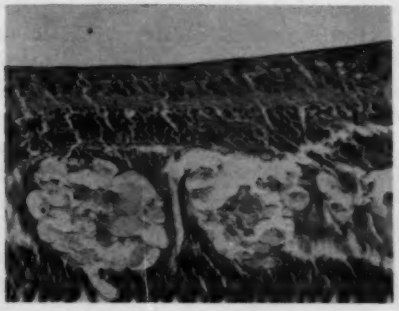
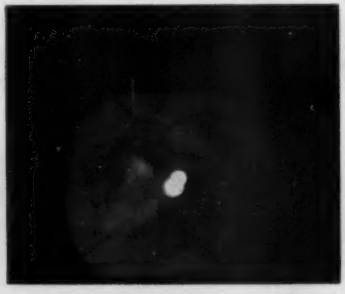


Fig. 3 (Case 1).—L. E., man, aged 59. Formerly gray elevated deep macular lesion, now coated with whitish layer, with deep hemorrhage adjacent to it. Same fundus as Figure 1, four years earlier.



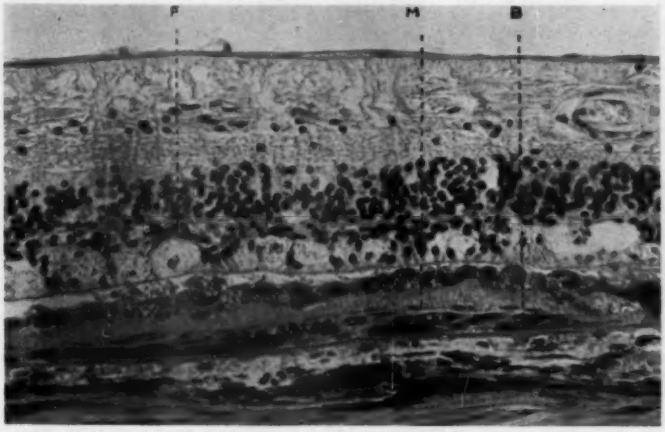


Fig. 4 (Case 3).—L. E., woman, aged 77, diabetic, eye lost from complications after corneal transplant. Macular lesion accompanying circinate retinopathy. Fibrous mound (*M*) like disciform degeneration, coated with layers of fatty granular cells (*F*) (appearing clinically white); *B*, Bruch's membrane. Hematoxylin and eosin; × 305.

small and lie at the ending of a macular arteriole or venule, indicating a former hemorrhagic episode.

The fourth type of whitish retinal opacities, cotton-wool patches, representing ischemic infarcts in the retina, rarely occur in the macular region and then only in its most peripheral aspects, since they lack the gravitational properties by which exudates and hemorrhages reach the avascular central macular zone.

Hemorrhages within the retina, no matter how deeply situated they are, can always be recognized as such, but not so their residua. When transport of hemosiderin-laden phagocytes within the retina is impaired, these pigmented cells may cluster around a blood vessel whose adventitia cells also participate in the pigment phagocytosis, and a dark-gray- or brownish-colored mound may result, such as was observed in the following case.

Case 2.—A man, 55 years of age, was examined with the ophthalmoscope just prior to his death, due to diabetic nephropathy. In the left macula there were massive white deposits in a circinate arrangement. The area inside of this ring appeared dark gray and in its inferior temporal aspect was markedly elevated, with a brownish cast to the color and with a few small overlying hemorrhages.

Sections through this inferior temporal portion of the macula (Fig. 6) revealed a markedly sclerotic arteriole surrounded by clusters of hemosiderin-laden phagocytes (positive iron stain) producing considerable thickening and prominence of the retina at its site.

Such areas could easily give rise to a suspicion of malignant melanoma unless accompanied, as in this case, by evidence of other disease.

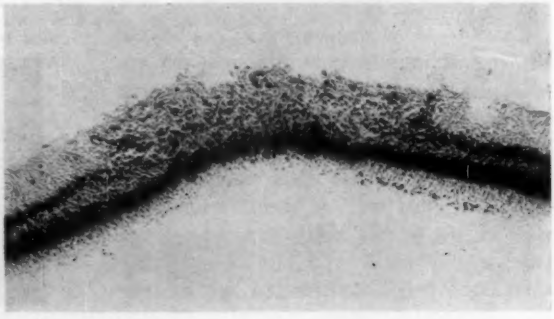


Fig. 5.—Glial scar in retina in old occlusion of central vein. The retinal pattern is destroyed within a circumscribed area. Dense neuroglial proliferation causes clinically visible yellowish opacity. Hematoxylin and eosin; × 170.

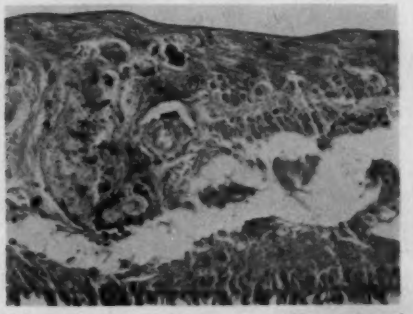


Fig. 6 (Case 2).—Same eye as Figure 2, region inside of circinate deposits. Sclerotic arteriole surrounded by hemosiderin-laden phagocytes which appeared clinically as elevated grayish-brown lesion. Colloidal iron-Van Gieson stain; × 135.

II. Cystic Appearance of the Macular Retina.—Several varieties of cystic-appearing macular lesions have been studied histologically, and their pathogenesis is now understood, while others still await clarification.

1. Detachment of the Internal Limiting Membrane: One of the commonest forms of cystic macular lesions occurs in the course of central serous retinopathy. It had been suspected for a long time (Gissy,[1] Guist[2]) and recently has been demonstrated histologically (Klien[3]) that the cystic appearance is due to a detachment of the internal limiting membrane by extravasation, usually of transudate but occasionally of hemorrhage, from the perimacular vessels.

The cyst is delicately but definitely outlined and is diagnostic of this condition, especially when the presence of hemorrhage raises the question of differentiating the condition from an inflammatory lesion, as in the following case.

Case 4.—A woman, aged 42, had noted blurring of the vision of the right eye for several weeks. At the time of the first examination the right eye could see the left third of each line down to 20/40.

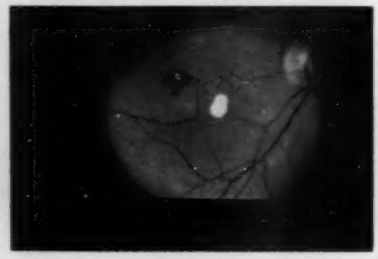
In the right fundus there was a grayish slightly elevated mass at the inferior nasal edge of the foveal region and the fovea itself was covered by a thin hemorrhagic veil (Fig. 7). In the reflected light a mottled appearance of the area adjacent to the gray lesion became visible, and the possibility of an inflammatory choroidal focus underneath the elevated gray area was considered. Only repeated inspection of the fundus revealed an inconspicuous but definite outline of a cystic area in the macula suggesting a central serous (angiospastic) retinopathy. After two months no residual findings in the fundus were left and the woman had regained normal right vision, a sequence of events supporting the diagnosis of functional retinal vascular disease.

The elevation of the cystic lesion caused by detachment of the internal limiting membrane may be slight and then is often associated with a distortion of the foveal reflex. This reflex may disappear altogether if the elevation becomes very marked.

Biomicroscopy may aid in the differential diagnosis of this and other cystic-appearing macular lesions. Its results, however, should be evaluated together with the other subjective and the objective features of the clinical picture, since, as some reports in the literature indicate, confusion is possible in the interpretation of some of the band-like reflecting zones of the posterior segment.

Figure 8 is a composite illustration of some of the findings in reflected light and of the biomicroscopic picture made several weeks after the onset of acute central serous retinopathy. The acute phase of this case was illustrated in Figure 1 in a previous publication (Klien[3]). At that time,

Fig. 7 (Case 4).—R. E., woman, aged 42, R. V. part of 20/40 line. Central angiospastic retinopathy with parafoveal hemorrhage. Note faint circular line around foveal lesion.



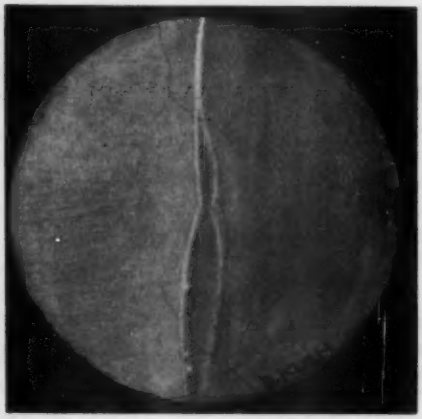


Fig. 8 (Case 5).—L. E., woman, aged 42, L. V. 20/40—3, central serous retinopathy with incipient choroidal participation, several weeks after acute onset. Composite illustration, left side showing finest folds visible in reflected light, right side showing biomicroscopic appearance. Retinal reflecting zone (right) bowing forward, indicating incipient retinal detachment; reflecting zone of detached internal limiting membrane (left) slightly umbilicated in center through adherence to retina at one place. Three punctate whitish deposits on outer surface of internal limiting membrane.

when vision in this eye was 20/30+3, there was a clear macular cyst with white dots sprinkled over its anterior wall and a central distorted foveolar reflex and there was no evidence of retinal detachment. Figure 8, which was made several weeks afterward, at a time when central vision had become reduced to 20/40−3, shows one slightly umbilicated reflecting band which represents the detached internal limiting membrane. At the point of umbilication, which probably corresponds to the fovea, this anterior band is still in contact with the posterior retinal band, which, however, at this place bows forward, indicating an incipient retinal detachment. The elevation of the cyst in this case was never very high, which accounts for the still-existing connection between internal limiting membrane and retina in the foveal area, very similar to the histopathologic findings in another case of central serous retinopathy (Fig. 9).

The left half of Figure 8 shows very fine folds which became visible in this region in reflected light. They were much more delicate than retinal traction folds and must have represented traction folds of the detached internal limiting membrane. I have observed them in a number of eyes in the subacute stage of central serous retinopathy or chorioretinopathy.

2. True Intraretinal Cysts: Transient intraretinal cysts may arise through exudation from temporarily diseased perimacular vessels such as must be assumed to exist in central syphilitis retinitis and conceivably also in other types of systemic diseases whose lesions have an affinity for the vascular system. Two clinical cases of such cysts, one of which was observed to rupture toward the vitreous cavity, and one histopathologic case of inner cyst rupture were discussed in a previous publication (Klien [4]). Rupture of such cysts, if it takes place at all, is probably commoner toward the subretinal space (outer cyst rupture), causing in that event a small central scotoma. Complete visual recovery indicates either absorption of the content without rupture or an inward rupture.

Permanent intraretinal cysts arise from a multitude of damaging influences upon the macular area, such as often-repeated attacks of functional vascular disturbances which finally result in some tissue destruction, toxic damage from chronic inflammatory processes in the anterior segment, progressive sclerosis of the perimacular arterioles, and many others.

Fig. 9 (Case 6).—R. E., man, aged 41, malignant melanoma of iris and ciliary body, central serous retinopathy, R. V. 20/50 at time of enucleation. Edema of retina in perifoveal region; extensive detachment of internal limiting membrane. Note remaining contact between it and the foveal retina, causing umbilication similar to biomicroscopic finding in Figure 8. Hematoxylin and eosin; × 135.

Fig. 10 (Case 7).—R. E., woman, aged 68, R. V. 20/100, progressively failing R. V. for two years; other eye normal. Cystic degeneration of macula. This type of lesion usually remains unilateral, in contrast to disciform and senile macular degenerations.

The cysts may remain small and give to the macular region a foamy appearance (Fig. 10), or there may be many small cysts surrounding a larger one, or one cyst may reach proportions such as to merit the term of retinoschisis (Fig. 11). All large macular cysts are potential macular holes, since a minor trauma may rupture both of their walls.

3. Circumscribed Detachment of Macular Retina: The appearance of a cystic elevation may also be produced by the detachment of the macular retina in the course of a serous chorioretinopathy or choroidopathy, especially when the subretinal fluid is clear. Biomicroscopy shows in such a case the characteristic separation of the centrally indented retinal reflecting band from the choroidal band (Amor's bow of Goldman). In a circumscribed macular detachment by hemorrhage the elevation appears very dark and of brownish color, and differential diagnosis of this condition and malignant melanoma is not always possible from the fundus picture alone unless the hemorrhagic mass changes its position and causes a noticeable alteration of shape and site within a short time.

4. Circumscribed Detachment of the Pigment Epithelium: Transudation from the choroid in the course of functional vascular reactions in the posterior polar region such as result in central serous chorioretinopathy or choriodopathy may accumulate at first between Bruch's membrane and the pigment epithelium, detaching the latter in a cystic fashion (Fig. 12). It is not known why in some instances the transudate accumulates immediately in the subretinal space and in others remains confined completely or for long periods to the space underneath the detached pigment epithelium. Perhaps the volume or the speed of transudation influences these events.

Clinically, the frequent appearance of iridescent lobulated figures (Gifford,[5] Klien[3]) within the macular lesions of the

Fig. 11 (Case 8).—L. E., man, aged 72, chronic postoperative iritis, epithelial downgrowth into anterior chamber after lens extraction. Marked cystic degeneration of macular region. Hematoxylin and eosin; × 33.

Fig. 12 (Case 9).—L. E., man, aged 50, L. V. 20/70, blurring vision noted for four to five weeks. Detachment of pigment epithelium; incipient detachment of retina in foveal region not shown here. Extramacular circumscribed flat idiopathic retinal detachment below disc clinically simulated a malignant melanoma and led to enucleation. This case will be published in detail. Hematoxylin and eosin; × 40.

Figure 11

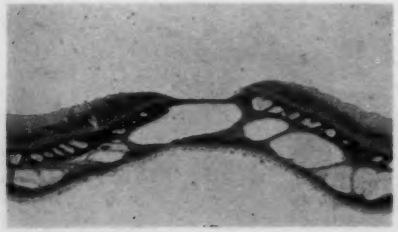
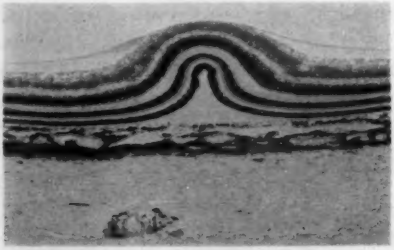


Figure 12



functional vascular disorders with choroidal participation may be significant. This silvery pattern, all of which seems to lie at the same level deep in or behind the retina, suggests an interference phenomenon caused by thin layers of fluid under tissue pressure. The most likely place for this phenomenon to arise is between the smooth and rigid membrane of Bruch and the pigment epithelium, especially since flat detachments of the pigment epithelium are demonstrable histologically in many conditions. For obvious reasons, no direct correlation between the clinical and histologic findings of this particular feature of the functional disease has so far been possible.

This glistening pattern is not always present, and it never accompanies a high cystic detachment of the pigment epithelium. The only clinical evidence of such detachment is a change in the refractive error toward hyperopia, with little or no decrease in the visual acuity, which can be demonstrated if the former refractive condition of the eye is known and its vision can be improved with convex lenses.

5. Vitelliform Macular Degeneration: One of the most striking cystic formations in the macular region accompanies the early stages of a hereditary degenerative macular process, which is probably not a primary degeneration of the first retinal neuron, since the striking clinical picture precedes by a year or more the first signs of a visual defect.

In the early stage the base of the clear cyst is formed by a homogeneous flat layer of a yellowish material which gives the lesion an egg-yolk-like appearance, hence the term vitelliform. The visual disturbance begins with the breaking up of this homogeneous material, flakes of which gradually fill the cyst. Later, the cyst ruptures and the remaining deposits of the flaky yellowish mass becomes mixed with clumps of pigment.

Falls,[6] Friedenwald,[7] and McFarland,[8] among others, have commented upon this condition and have reported pertinent clinical cases. No histopathologic examination of the cystic stage has been made so far. Both Friedenwald and Falls suggest the pigment epithelium as the site of the yellowish-white discoloration of unknown pathogenesis.

The Pigment Epithelium

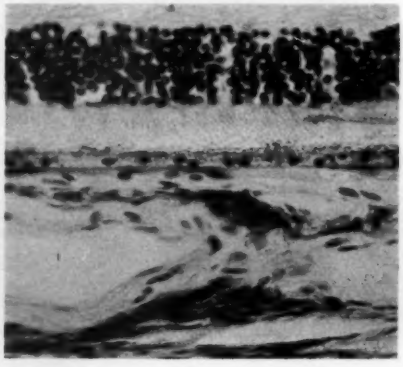
An integral part of the retina developmentally, the pigment epithelium, like the outer avascular half of the retina, depends for its nutrition entirely upon an intact capillary layer of the choroid. It is damaged at an early stage in the course of choroidal disease, whether inflammatory, traumatic, or degenerative in nature.

Less-well-appreciated is the fact that abnormal processes in the inner layers of the retina, especially those associated with widespread edema, may also produce extensive alterations of the pigment epithelium. The pigmented residua of central serous retinopathy or of juxtapapillary retinopathy are representative of such instances.

Various histologic specimens reveal the pigment epithelium as one of the most versatile structures in its responses to irritation by noxious agents and mechanical factors or to malnutrition. Its most frequent alterations will now be discussed.

1. *Depigmentation in Situ.*—Without disturbance in the continuity of the layer the

Fig. 13.—Within a circumscribed area pigment epithelial cells are flatter than normal, irregularly spaced, and contain little pigment. Sclerosis of large choroidal arteries, choriocapillaris intact; × 450.



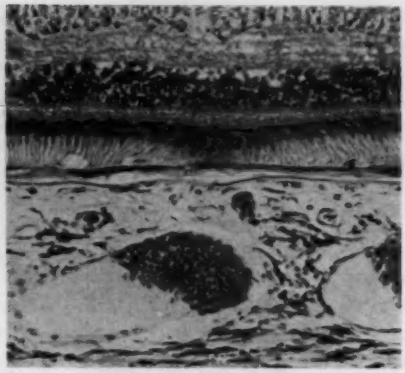


Fig. 14.—Incidental finding of circumscribed atrophy of choriocapillaris with corresponding localized degeneration of pigment epithelium and incipient degeneration of rods and cones. Hematoxylin and eosin; × 240.

individual cells lose some or all of their pigment and become flatter than normal (Fig. 13). In such areas their physiologic activity is probably severly curtailed without necessarily ceasing altogether. Some reductions of central vision might be explained by such patches occupying the macular region.

Clinically, depigmentation in situ is indicated by gradually expanding ill-defined areas within which the choroidal vascular pattern becomes increasingly distinct over a period of months or years. It may be observed in advanced old age, with or without visible choroidal vascular sclerosis, and in high myopia. It is possibly a precursor of senile macular degeneration, since many transitions from simple depigmentation in situ to more marked degeneration of the pigment epithelium with incipient or advanced destruction of the percipient retinal elements may be encountered (Figs. 14 and 15).

2. *Simple Proliferation.*—Circumscribed heaps and mounds of proliferated pigment epithelial cells which remain confined to the subretinal space may be produced by many incidental localized irritations, originating from either the choroidal or the retinal side. They may reach considerable size and clinically may simulate pigmented tumors. Typical lesions of this kind, of retinal origin, are encountered after repeated attacks of central serous retinopathy; a choroidal disturbance is certain to be the cause of the clusters of pigmented cells in Siegrist's bead-string pigmentation over markedly sclerosed choroidal arteries in hypertension and very probable for the circumscribed pigment proliferations in high myopia clinically visible as Fuchs' spots (Fig. 16).

The cells composing these mounds may gradually lose their pigment content, undergo atrophy, and flatten into spindle cells. Thus, it is possible to observe clinically over a period of years a change in color from the deep brown of the recent lesion to the grayish or yellowish-white color of fibrotic residua.

3. *Proliferation in Response to Demand for Phagocytes.*—In many retinal diseases characterized by relative chronic anoxia, such as the diabetic and hypertensive retinopathies and Coats' disease, rapid proliferation of pigment epithelial cells often results in large numbers of faintly pigmented or nonpigmented phagocytes in the subretinal space and in the outer retinal layers which become one of the main sources of fatty granular cells (Figs. 2 and 4).

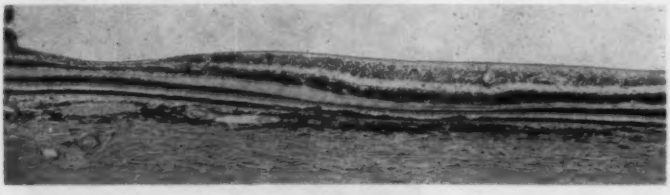


Fig. 15 (Case 12).—L. E., woman, aged 89, postmortem specimen. Incipient senile macular degeneration. Circumscribed degeneration of rods and cones of inferior macular area, corresponding to similarly circumscribed area of degeneration of pigment epithelium and of choroidal atrophy. Hematoxylin and eosin; × 56.

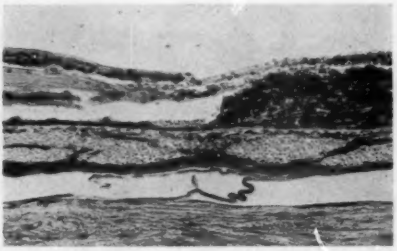


Fig. 16 (Case 13).—L. E., man, aged 50, unilateral high myopia, eye lost from penetrating injury in anterior segment. Mound of proliferated pigment epithelial cells found in subretinal space in foveal region, would clinically appear as pigmented elevation like a Fuchs spot. Hematoxylin and eosin; × 70.

4. *Proliferation with Formation of Cuticular Masses.*—In this form of proliferative activity of the pigment epithelium, which occurs in children and young adults, multiplication of its cells is associated with production by these cells of large masses of a cuticular substance, similar to that of the inner cuticular portion of Bruch's membrane.

Inflammation, exudative or hemorrhagic processes, or trauma in the young may give rise to this activity, which often results in tremendously large globular masses consisting of alternating layers of a glassy substance and rows and tubules of new-formed pigment epithelial cells. Occasionally, such a formation is encountered as an isolated lesion of obscure origin with a predilection for the macular region, without any other obvious ocular disease. The latter variety may be congenital, but even so it has been noted to grow in size during later life, a feature which rouses suspicion of a malignant tumor and usually leads to removal of the eye. The following case illustrates this type of pigment epithelial activity and some of the problems engendered by it.

Case 14.—A youth, 19 years of age, had first noted impairment of the vision of his left eye five weeks prior to its enucleation.

The left vision was 20/50; the right vision and the right eye were normal. In the left fundus there was an elevated pigmented lesion, below the foveal region, about 1 d. d. in size, surrounded by a zone of yellowish discoloration (Fig. 17). The fovea appeared distorted as a result of traction upon the retina from the mass below, and there were numerous traction folds radiating upward from the lesion.

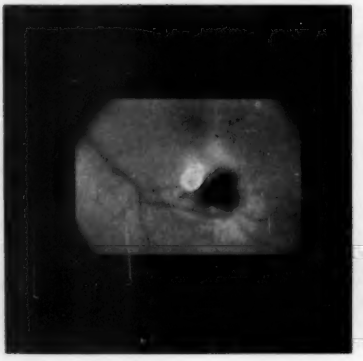
The eye was removed elsewhere, with the diagnosis of malignant melanoma of the choroid.

Histopathologic examination revealed a mass of cuticular substance mixed with proliferated pigment epithelial cells which were particularly dense over its inner surface, explaining the dark brown color of the fundus lesion. At its site the mass had completely replaced the retina, its inner surface protruding above the inner retinal level. It was surrounded by specific granulation tissue composed of epithelioid cells and lymphocytes, which had infiltrated the adjacent retina and the underlying choroid (Fig. 18).

Many preretinal precipitates were scattered over the inner surface of the macular retina, and smaller precipitates were suspended in the posterior half of the vitreous.

The findings of greatest differential diagnostic value in the clinical picture of this fundus were the signs of traction in the retina surrounding the lesion and the broad zone of homogeneous yellowish discoloration, together with the small size of the lesion. A small malignant melanoma does not infiltrate the retina, and only cellular

Fig. 17 (Case 14).—L. E., youth, aged 19, L. V. 20/50, elevated pigmented lesion below fovea. Note faint traction folds running over foveal area.



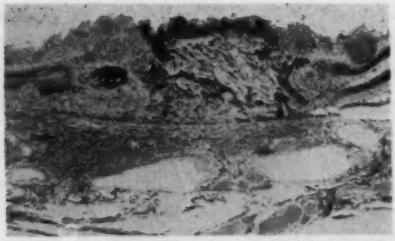


Fig. 18.—Same eye as Figure 17, histologic section. Retina interrupted by mass of cuticular substance and rows of proliferated pigment epithelial cells. Retina on each side of it, and underlying choroid, are infiltrated with specific granulation tissue, clinically causing yellowish zone around pigmented lesion. Hematoxylin and eosin; × 39.

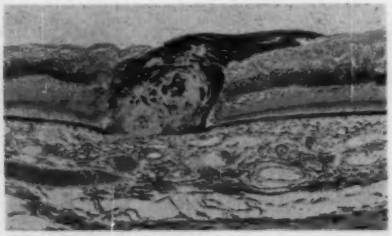


Fig. 19 (Case 15).—R. E., youth, aged 17, contusion and perforating injury of anterior segment by exploding bottle eight years previously. Foveal retina replaced by mass of cuticular substance with rows and plaques of proliferated pigment epithelium, similar to that shown in Figure 18 of inflammatory origin. Clinical picture would have been very dark brown elevated lesion. Hematoxylin and eosin; × 41.

infiltration or shrinkage of intraretinal fibrous scar tissue could produce these delicate folds. When a malignant melanoma causes retinal folds, it is through tenting of the retina by its large size.

Use of the biomicroscope might have revealed the vitreous opacities and preretinal precipitates, which would have definitely pointed to an inflammatory condition.

The traumatic origin of such a lesion is illustrated in Figure 19.

5. *Proliferation with Metaplasia.*—In long-standing diffuse retinal or chorioretinal disease thick membranes of neuroglia or fibrous tissue may develop between choroid and retina and replace the neuroepithelium and often portions of the pigment epithelium and may be traced to a proliferative activity of the latter in the earlier stages of the disease. A macular lesion of this kind, consisting of a glial plate which had replaced the percipient retinal elements and which had given the foveal area a punched-out appearance clinically, was described in a case of amaurotic idiocy in a previous publication (Klien[9]).

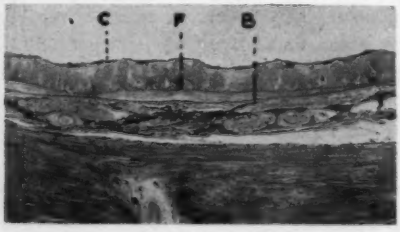
Glial masses in the choroid, which have entered through a gap in Bruch's membrane and which may be traced to the pigment epithelium at the edge of an old chorioretinal scar, are not an uncommon finding (Fig. 20).

Clinically such a finding may be suspected when an old chorioretinal scar is surrounded by a yellowish well-defined zone which does not change its size or shape thereafter.

6. *Hyperactivity Without Proliferation.*—In addition to the localized hyperactivity

Fig. 20 (Case 16).—R. E., girl, aged 3½, keratitis at birth, buphthalmos, malformation of optic nerve. Illustration shows half of a large atrophic chorioretinal scar in macula. At edge of scar, proliferation of pigment epithelium into choroid with metaplasia into neuroglia tissue. Hematoxylin and eosin; × 130.

Fig. 21 (Case 17).—R. E., woman, aged 62, gradual painless failure R. V. over a period of 15 years; pain in previous 3 months following intraocular hemorrhage. Pigment epithelium flat and degenerated; underneath it, diffuse thick layer of cuticular substance (*C*). Between this layer and Bruch's membrane (*B*) two mounds of newformed fibrous tissue (*F*) representing disciform macular degeneration. Van Gieson; × 40.



which results in the well-known drusen of Bruch's membrane, an occasional instance of diffuse hyperactivity which seems to represent a protective mechanism is of special interest.

In degenerative diseases which are associated with dehiscences of Bruch's membrane, such as disciform macular degeneration, angioid streaks, and even advanced old age, one often encounters thick plaques of a homogeneous cuticular substance which merge with the inner cuticular portion of the membrane over large areas and particularly over macular lesions of choroidal origin (Fig. 21). The continuity of the pigment epithelium, so important for the visual function, is endangered by damage to the lamina basalis and its diffuse overactivity could be interpreted as largely reparative.

Comment

The foregoing data may be readily applied to some of the problems inherent in the differential diagnosis of the various macular lesions. It is perhaps surprising but definitely helpful that most of the tissue responses in the retina and pigment epithelium described above do not occur, as a rule, in malignant melanoma, a fact which deserves emphasis. Features to be stressed are the following:

In Malignant Macular Melanoma

1. Absence of lipoid deposits indicative of relative chronic anoxia or edema residues in overlying retina.

2. Absence of whitish lipoid coating of deep-seated elevation.

3. Absence of traction folds of the fine and finest variety, either radial or concentric. When tumor has reached considerable size and retinal detachment is not high, coarse traction folds may arise through tenting of the retina by prominence of the tumor.

4. Absence of vitreous opacities or preretinal haze (including biomicroscopic examination).

5. Usually, absence of hemorrhage in the early stages; if present, it is not in the form of a collarette or of the well-defined coin-shaped type, but as small flat hemorrhages over the elevation itself. Later, massive retinal hemorrhage may result from expansion of tumor into optic nerve and occlusion of venous branches.

6. The lesion does not change its shape rapidly.

7. The lesion does not change its position.

8. If pigmented, the lesion remains so.

9. Second tumors in the same eye or in the fellow eye are very rare.

10. Outline of lesion becomes usually more indistinct with increase in its size, owing to adjacent detachment of retina.

In Macular Lesions Other Than Tumor

1. Lipoid deposits in overlying retina are common in subacute inflammation and lesions of vacular origin, functional or organic.

2. Whitish lipoid coating of deep-seated mounds, such as those of disciform degeneration and of circinate retinopathy, may be observed.

3. Traction folds are common. They may appear in the form of radial, parallel, or concentric circular lines.

A. Radial or parallel lines: (*a*) The finest occur in detachment of the internal limiting membrane, best seen in reflected light, in functional retinal vascular disorders. (*b*) Fine folds often accompany massive cellular infiltration of the retina in active inflammation, which tenses the surrounding normal tissue, or intraretinal scarring of inflammatory origin.

B. Concentric circular lines are usually due to edematous imbibition, which increases the physiologic prominence of the macular area over the level of the adjacent uninvolved retina, such as occurs in functional vascular disturbances.

4. Vitreous opacities, preretinal precipitates, and preretinal haze are encountered in inflammatory lesions.

5. Hemorrhages are common (*a*) as collarette around inflammatory foci; (*b*) as well-defined flat coin-like areas, a disc diameter or more in size, resulting from hemor-

rhages into foveal cysts in organic disease of the perimacular vessels; (*c*) as ill-defined elevated dark-brown areas, 1 to 3 d. d. or more in size, resulting from retroretinal hemorrhage in the course of functional or organic choroidal or chorioretinal vascular disease.

6. A lesion may change its shape and even its position rapidly and unexpectedly from the effect of gravity upon a massive subretinal hemorrhage or exudate. Daily careful inspection of such a lesion is often a revealing procedure.

7. Pigmented lesions may gradually loose their pigment content when due to simple proliferation of the pigment epithelium, which undergoes metaplasia into fibrous tissue. This event is not uncommon after repeated functional disturbances of the perimacular retinal vessels and in myopic degeneration of the posterior polar region.

8. Lesions similar in appearance to the macular involvement in other locations in the same and/or in the fellow eye are frequent in inflammatory disease and are occasionally encountered in functional disorders of the retinal or choroidal vessels.

9. Lesions of the macula in the fellow eye are the rule in the disciform degeneration, senile degeneration, and the heredodegenerations of the macula.

10. Increasing distinctness of outline of a lesion in spite of increasing size and, subjectively, of further enlargement of the central scotoma occurs as a rule in the disciform macular degeneration and in the hemorrhagic type of the functional choroidal vascular disease, two conditions which may pose the most difficult problems in the differential diagnosis of malignant melanoma.

Conclusion

Retina and pigment epithelium and, to a less extent, the choroid react often characteristically in the course of certain disease processes. The formidable difficulties encountered in the differential diagnosis of macular lesions of inflammatory, degenerative, and vascular origin from each other, on the one hand, and from malignant melanoma, on the other, are lessened by knowledge of some of the basic tissue responses in this region and of their correlated clinical manifestations.

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Ocular Signs and Prognosis in Subdural and Subarachnoid Bleeding in Young Children

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The problems of subdural hematoma and subarachnoid hemorrhage in infancy have been thoroughly discussed in recent years in the pediatric, neurologic, and neurosurgical literature. The following analysis of 47 patients seen and followed at the Mayo Clinic during an 11-year interval emphasizes the ophthalmologic manifestations and sequelae. The neurologic abnormalities other than those of ophthalmologic interest have been reported elsewhere.[1]

Subhyaloid and retinal hemorrhage associated with subdural and subarachnoid bleeding among adults is well known.[2-8] The occurrence of such hemorrhage among children with these conditions has been pointed out.[9-15] Ingraham and Matson [12] reported that intraocular hemorrhage occurred in 21.8% of a large series of infants who had subdural hematomas. Govan and Walsh [13] found such hemorrhage in 50% of their infant patients. Statten [14] noted retinal hemorrhage in 21 (75%) of 28 infants. Guthkelch [15] reported that 20% to 25% of 24 such patients had changes in the fundus oculi. Among children this hemorrhage tends to be in the form of massive extravasation, which later resorbs. We reviewed our records of such patients to evaluate the extent of permanent ocular damage resulting from the intracranial bleeding.

Present Study

This report concerns 47 of the 54 cases of proved subdural hematoma, subdural hygroma, and subarachnoid hemorrhage occurring among children 5 years of age or less seen at the Mayo Clinic from 1945 through 1955. Seven of the fifty-four cases were excluded from this study because an examination after mydriasis was not done by an ophthalmologist. The diagnosis was confirmed by examination of cerebrospinal fluid in the 10 cases of subarachnoid hemorrhage or by an intracranial procedure in the 31 cases of subdural hematoma and the 6 cases of subdural hygroma.

Sex and Age.—The 47 patients included 31 boys and 16 girls (2:1). Ingraham and Matson [12] reported a ratio of 1.7:1. A total of 39 of the 47 patients were less than one year of age. The mean age was 6 months. Most authors have noted that the peak incidence of these lesions among children is in patients less than one year of age. Govan and Walsh [13] ascribed this high incidence to the poorly developed supporting tissues around the intracranial vessels in infants of this age.

Symptoms and Signs.—The presenting symptoms consisted chiefly of convulsions (40% of the patients) and vomiting (32%). An enlarging head, paralysis, spasticity, and stupor were found in a smaller number. Ocular abnormalities were the predominant signs in our series, being present in 60% of the 47 patients.

Etiology.—Positive or possible histories of trauma were noted in 23 of the 47 cases. Among these patients subjected to trauma, those who had normal eyes were about equal in number to those who had ocular pathologic changes. The intracranial bleeding was ascribed to a blood dyscrasia in three pa-

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tients. No history relevant to a cause could be elicited in the remaining 21 patients.

Ocular Manifestations.—As already mentioned, 28 (60%) of the 47 patients seen by ophthalmologists had abnormal ocular signs, whereas 19 had normal eyes. The abnormal ocular findings consisted predominantly (24 patients, or 51%) of numerous zones of subhyaloid and retinal hemorrhage. Sometimes there were several areas of hemorrhage the size of the optic disc or larger, but usually the hemorrhage was even more severe. Intraocular bleeding frequently was massive, and the hemorrhagic zone often covered the entire posterior pole of the globe. The bleeding was so severe at times that the retinal structures could not be seen through the thick layer of blood. In no case did the hemorrhage enter the vitreous body in the fashion sometimes observed among adults with subarachnoid hemorrhage.

Characteristically, the blood in the eyes showed signs of beginning absorption as early as one week after the intracranial lesions were treated. Improvement continued in each case until the blood was completely absorbed. Healing usually was complete, and no traces of the previous hemorrhage remained. Slight mottling of the retinal pigment was noted in the more severely involved eyes. Two patients, one seen five years later and the other three years later, had no evidence of retinal disturbance but had a peculiar green-blue-red "rainbow" reflection in the macular region; this was thought to result from retained blood pigments in the vitreous or at the internal limiting membrane of the retina.

Of the 24 patients who had intraocular hemorrhage, 5 had papilledema and 5 had palsy of cranial nerves. Both sixth nerves were affected in two of the latter patients, whereas the right sixth nerve was involved in one and the third nerve in two. Two of the twenty-eight patients who had ocular abnormalities had papilledema without retinal hemorrhage, and the remaining two patients had palsy of the sixth cranial nerves without retinal hemorrhage (Table 1).

The bleeding was bilateral in 17 of the 24 patients who exhibited intraocular hemorrhage, whereas 4 patients had bleeding into the right eye only and 3 had bleeding into the left eye only. The sex distribution was equal among those with or without intraocular hemorrhage. The presence or absence of intraocular hemorrhage did not appear to be related statistically to the severity of the presenting symptoms. However, the predominant ocular abnormalities were found among the patients who had either subdural hematoma (65%) or subarachnoid hemorrhage (70%); such abnormalities were unusual among the patients who had subdural hygroma (17%).

We compared the incidence of intraocular hemorrhage among patients who had subdural hematoma, those who had subarachnoid hemorrhage, and those who had subdural hygroma (Table 1). Of the 31

TABLE 1.—*Ocular Abnormalities in Forty-Seven Children with Intracranial Bleeding or Hygroma*

Ocular Abnormality	Patients	Intracranial Lesion		
		Subdural Hematoma	Subarachnoid Hemorrhage	Subdural Hygroma
Retinal hemorrhage	24			
Alone		12	3	1
With papilledema		3	0	0
With palsy of extraocular muscles		1*	2†	0
With papilledema & palsy of extraocular muscles		0	2‡	0
Palsy of extraocular muscles	2	2§	0	0
Papilledema	2	2	0	0
No ocular defects	19	11	3	5
Totals	47	31	10	6

* Third-nerve palsy.
† One with bilateral sixth-nerve palsy and one with third-nerve palsy.
‡ One with bilateral sixth-nerve palsy and one with right sixth-nerve palsy.
§ Both with sixth-nerve palsy.

TABLE 2.—*Relation of Duration of Symptoms of Intracranial Lesions to Retinal Findings*

Duration of Symptoms	Retinal Findings	
	Retinal Hemorrhage	Normal Fundi
Less than 24 hr.	10	5
1 to 13 days	7	8
2 wk. to 2 mo.	5	8
2+ mo.	2	2

patients who had subdural hematoma, 16 (52%) had retinal hemorrhage either alone (12 patients) or associated with papilledema (3 patients) or with palsy of extraocular muscles (1 patient). Seven of ten patients who had subarachnoid hemorrhage had retinal hemorrhage alone or associated with papilledema and palsy of extraocular muscles. Only one of the six patients who had subdural hygroma had retinal hemorrhage.

Govan and Walsh [13] considered that little was gained by subdividing subdural hematomas into acute and chronic types, and Munro [16] stated that such division was unnecessary and artificial. We compared the relative frequency of intraocular hemorrhage in the more acute and fulminating disease and in that of longer duration. No correlation was evident between the presence of intraocular hemorrhage and the duration of symptoms (Table 2).

The incidence of permanent ocular damage was considerably greater among patients who had sustained known trauma than it was among those who had not. Fifteen (54%) of the twenty-eight patients who initially had ocular defects and eight (42%) of the nineteen patients who had normal eyes had intracranial bleeding as a result of trauma. Thus, as already noted, about half of the total group had histories of trauma.

Four of the seven patients who died during the first two years after onset of the intracranial lesion had sustained injuries. One of these had intraocular hemorrhage, and three, including one with hemophilia, had normal eyes. Of the three patients without histories of trauma who died during the first two years, one had normal eyes and two, including one with purpura, had intraocular hemorrhage.

Visual Prognosis.—The visual prognosis among infants and small children sustaining intraocular bleeding associated with intracranial hemorrhage has not been reported in the literature in a series large enough to assure validity. As just noted, 7 of our 47 patients died within two years of admission. The information in the clinic records in the remaining patients was supplemented by follow-up letters to parents, guardians, or physicians. Of the 40 who survived, 38 were followed from 1 to 10 years, with an average follow-up period of 5 years. Among these 38 patients, 13 (34%) had permanent physical defects, including 9 who had visual abnormalities either as their only residual or associated with other physical defects (Table 3).

Of the 19 patients who had normal eyes, 4 died. The remaining 15 were examined or traced. Of these, only one had residual ocular lesions. This was a patient who had birth injuries and was first examined at the age of 2 months. A diagnosis of bilateral subdural hematoma was made. According to the last report, the patient was totally blind at the age of 5 years.

TABLE 3.—*Relationship of Initial Ocular Signs of Prognosis*

Condition of Eyes at Initial Examination	Total Patients	Follow-Up Data			
		Died	Permanent Physical Defects	Essentially Normal	Untraced
Abnormalities present					
With retinal hemorrhage	24	3	9	10	2
Without retinal hemorrhage	4	0	2	2	0
Normal	19	4	2	13	0
Totals	47	7	13	25	2

TABLE 4.—*Incidence of Permanent Ocular Defects in Twenty-Three Surviving Traced Patients with Initial Ocular Damage*

Case	Cause	Age	Initial Ocular Findings	Intracranial Lesion	Permanent Ocular Defects	Age at Last Examination, Yr.
1	Skull fracture	11 mo.	Large intraocular hemorrhage, right	Bilateral subdural hematoma	Total blindness	7
2	Auto accident	2 mo.	Third-nerve palsy, right; intraocular hemorrhage, left	Subarachnoid hemorrhage	Optic atrophy & total blindness	9
3	Auto accident	4 yr.	Intraocular hemorrhage & papilledema, both eyes; bilateral sixth-nerve palsy	Subarachnoid hemorrhage	Pallor both optic discs and probable paracentral scotomas, both eyes; vision: R. 20/70; L. 20/20	12
4	Unknown	3 yr.	Right sixth-nerve palsy	Bilateral subdural hematoma	Right amblyopia and esotropia; vision: R. 20/70; L. 20/20	8½
5	Birth trauma	42 hr.	Mild retinal hemorrhage	Subarachnoid hemorrhage	Alternating esotropia 30 to 40 degrees due to bilateral sixth-nerve paresis	5
6	Fall	5 mo.	Retinal hemorrhage & papilledema, both eyes	Bilateral subdural hematoma	Mild amblyopia, left	8
7	Fall	17 mo.	Hemorrhage both retinas; partial left third-nerve palsy	Left subdural hematoma & subarachnoid hemorrhage	Deep amblyopia and exotropia, left; vision: R. 20/25; L. counts fingers	9
8	Unknown	4 mo.	Preretinal hemorrhage, both eyes	Right subdural hematoma	Amblyopia & exotropia, right eye; after muscle surgery, amblyopia of left eye; vision: R. 20/20; L. 20/50	9

Of the 28 patients who had ocular abnormalities, 3 died. A total of 23 of the remaining 25 were examined or traced. Of these, eight (35%) had permanent visual handicaps (Table 4). Three of the seven patients who had initial palsy of extraocular muscles had permanent visual handicaps.

Among the nine patients who sustained permanent residual ocular defects, seven originally had experienced known trauma. Three of these nine patients sustained severe cerebral damage and were greatly retarded, spastic, or completely incapacitated.

Comment

In this study, half of the infants and young children who had subdural hematoma and 70% of those who had subarachnoid hemorrhage had extensive retinal and subhyaloid hemorrhage. A small additional group had palsy of extraocular muscles or papilledema with or without associated intraocular hemorrhage. None of our patients had pathologically pale optic discs at our initial examination, although pale discs developed later in two patients. This is at variance with other reports, in which the incidence of pale discs is usually high. We agree with Walsh,[17] who considered that the normal pale state of the discs of infants is often erroneously thought to be pathologic pallor. Thus, we believe that many of the patients with pale discs reported on in the literature may have had normal fundi, although a small number of such patients might be expected to have optic atrophy secondary to chronic increased intracranial pressure or to hemorrhage into the sheath of the optic nerve.

Retinal and subhyaloid hemorrhage in infants is strong evidence that either subdural hematoma or subarachnoid hemorrhage is present. This situation is different in adults, in whom such hemorrhage is a characteristic sign of subarachnoid bleeding but does not usually appear with subdural hematoma. Papilledema is the more frequent ophthalmoscopic picture of subdural hematoma in adults. The open fontanels and the separated sutures in the infant apparently offset any gradual increase in intracranial pressure. Hence, only sudden increases of intracranial pressure are reflected in the ocular fundi. This

may account for the greater frequency of intraocular hemorrhage in infants.

We could find no ophthalmoscopic features that would distinguish subdural hemorrhage from subarachnoid hemorrhage in infants. Both lesions were associated predominantly with massive retinal and subhyaloid hemorrhage. A few patients had papilledema with or without intraocular hemorrhage. The incidence of intraocular bleeding was somewhat greater among patients who had subarachnoid hemorrhage than it was among those who had subdural hematoma, and the incidence of intraocular hemorrhage was low among the children who had subdural hygroma.

It is important to know that the prognosis for ultimate binocular vision is not uniformly good among those infants who have ocular abnormalities at the time of the initial examination. As already noted, our study showed permanent visual impairment in 8 of the 23 surviving patients followed in this group but in only 1 of the 15 traced survivors who did not have ocular abnormalities. Seven of the eight patients in the former group who had residual ocular abnormalities had intraocular hemorrhage, and one had an isolated palsy of the sixth nerve. The preponderant permanent ocular defects appeared among those patients who had sustained trauma to the head. Pediatricians, neurosurgeons, and ophthalmologists should be aware of this fact, as the prognosis for permanent visual recovery may not be good in some cases.

Summary

A study was made at the Mayo Clinic of the ocular findings in 47 cases of subdural hematoma, subdural hygroma, and subarachnoid hemorrhage in infants and young children. Pathologic ocular findings were present in 28 (60%) of the cases, with large zones of retinal and subhyaloid hemorrhage being the predominant ocular lesion in 24 instances. Palsy of extraocular muscles or papilledema was present in other cases.

Follow-up studies revealed that 8 of the 23 traced surviving patients who had ocular abnormalities at the time of intracranial bleeding had permanent ocular defects, whereas only 1 of the 15 traced survivors who did not have ocular defects at the time they sustained intracranial bleeding had permanent ocular damage.

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The Prognosis of Primary Tumors of the Iris Treated by Iridectomy

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Over the years it has become increasingly evident that tumors of the iris should not be lumped with those of the ciliary body and choroid. They present entirely different problems in clinical diagnosis and surgical management, and there is mounting evidence to support the belief that biologically they may be different tumors. Progress in the study of these tumors has been slow, for they are not common, and a large volume of material with many years of follow-up is necessary for the accumulation of a series of cases from which lessons can be learned. Reese,[1] for example, stated that at the Institute of Ophthalmology, in New York, 271 malignant melanomas of the uvea included only 23 that were primary in the iris. More recently, Duke and Dunn[2] reviewed the primary tumors of the iris in the pathology laboratory of the Wilmer Institute and were able to report only 43. Even so, their series represents the largest published to date. The Registry of Ophthalmic Pathology, with its large collection of about 45,000 cases, has also furnished little information on tumors of the iris. A number of years ago, when Callender, Wilder, and Ash[3] presented a five-year follow-up study of 500 melanomas of the choroid and ciliary body in the Registry, they had comparatively little to offer about iris tumors, for they had only 32 cases. Now the collection has grown, and, although the ratio of tumors of the ciliary body and choroid to those of the iris is still about 15:1, a sufficient number of the latter have been followed for periods long enough to make us confident that we have an understanding of their natural behavior.

The pathologic anatomy of these peculiar tumors can be learned only from a sizable group of cases. When a few random sections from a small series are studied, differences are likely to be impressive and given exaggerated and undeserved significance. Some of the tumors are deeply pigmented and diffuse; others are discrete and spindle-shaped and closely resemble leiomyomas of mesenchymal tissues. Are these seemingly different tumors related?

In the iris, over one-half of the tumors treated surgically are sufficiently localized to be amenable to local excision by iridectomy. Similar excisional therapy is rarely possible for tumors in the choroid or ciliary body. It is our purpose in this paper to evaluate the results of iridectomy for localized tumors of the iris. How often can they be treated successfully by such conservative therapy? How often and for what reasons does it become necessary to enucleate the eye? Are these iris tumors really malignant, and how often do they metastasize?

Materials and Methods

All cases selected for this study were drawn from the Registry of Ophthalmic Pathology of the Armed Forces Institute

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From the Registry of Ophthalmic Pathology, Armed Forces Institute of Pathology. Director, Ophthalmic Pathology Laboratory, Washington Hospital Center (Dr. Rones); Pathologist-Specialist, Veterans' Administration Central Laboratory for Pathologic Anatomy and Research, and Chief, Section on Ophthalmic Pathology, Armed Forces Institute of Pathology (Dr. Zimmerman).

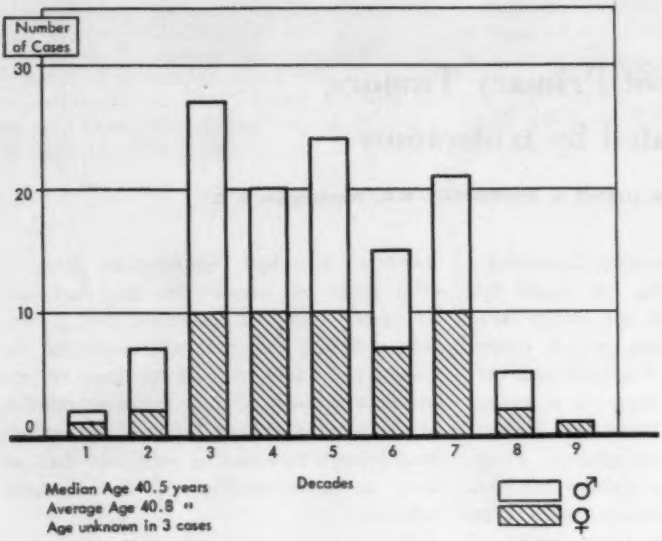

Fig. 1.—Age at time of iridectomy in 125 patients with tumors of the iris.

of Pathology. The criteria for selection were (1) that iridectomy had been the initial surgical procedure for treatment of a localized tumor, (2) that sections of the tumors were available for review, and (3) that in our opinion the tumor belonged in the broad category of melanotic or potentially pigmented neoplasms. One hundred twenty-five cases, representing about half the total iris tumor material on file at the A. F. I. P., met these criteria. The ophthalmologists and pathologists who had contributed the cases to the Registry were asked to furnish additional clinical data and follow-up information. Pertinent clinical and pathologic data have been tabulated and are analyzed in this paper.

Results

Age.—This study has confirmed the general impression that patients who have melanomas of the iris are younger than those who are treated for tumors of the posterior uveal tract. Reese[1] stated that the average age of patients with malignant melanomas of the iris is 10 to 20 years younger than that of patients with malignant melanoma elsewhere in the uvea. The average age in his series is 46 years. The average age in the Wilmer series[2] is 42 years. Figure 1, a chart of the age distribution at the time of iridectomy in our series, indicates that the average age is 40.8 years, with a median age of 40.5 years. Yet this does not give the whole picture, since many patients were aware that the tumor had been present for years before operation (Table 1). The ages of other patients at onset could not be determined, since in a third of the cases the patient had not been aware of the lesion until shortly before operation (Table 2). Furthermore, many of those who realized that a lesion was present could not state exactly when it had first appeared. It is significant, however, that a number of tumors had been noted during childhood (Table 1), and in four instances iridectomy

TABLE 1.—*Duration of Tumor Prior to Iridectomy*

	Cases, No.
Recently discovered	48
1 to 5 yr	30
5 to 10 yr	9
10 to 40 yr	13
"Congenital," "since childhood"	7
"Many years," "long as I can remember"	6
No information	12
Total	125

TABLE 2.—*Patient's Awareness of Tumor*

	Cases, No.
Chief complaint: iris tumor	67
Aware of lesion (other chief complaints)	11
Patient unaware of tumor	41
No information	6
Total	125

had been performed before the patient was 15 years of age. Abstracts of these four cases follow.

CASE 1 (A. F. I. P. Acc. 75975) (Reported by Zentmayer in 1930).—A 10-year-old boy was seen because of small pink growth in the lower outer quadrant of his left iris. The lesion had seemed to grow larger in the four months since it was first noticed. The ovoid tumor, which measured 3×5 mm., rested on the anterior surface of the iris at the smaller circle and protruded into the pupillary space. It was covered by ramifying vessels, smaller than those of the iris elsewhere. The iris, except for the sector on which the tumor rested, reacted to light. Wide iridectomy was performed. Bleeding was profuse during the operation, but good results were obtained.

Histopathologic examination by Drs. P. De Long and J. McFarland led to a diagnosis of "leukosarcoma." Our review of the sections revealed a virtually nonpigmented but cellular tumor which protruded prominently from the anterior surface of the iris stroma. The tumor cells were slender and spindle-shaped and in several places appeared to be arranged with their nuclei radiating from prominent, dilated blood vessels which coursed throughout the nodule. Elsewhere a fascicular pattern was produced by parallel alignment of the tumor nuclei. The nuclei themselves were rather pale-staining and did not contain nucleoli. The tumor was regarded as a spindle-A variety of amelanotic melanoma, which exhibited leiomyomatous differentiation. A fairly large segment of iris peripheral to the nodule was not involved, and several ciliary processes were seen. Postoperatively the eye was irradiated, but it was not enucleated.

At follow-up examination three and one-half years later the tumor had not recurred.

CASE 2 (A. F. I. P. Acc. 559162).—A white girl, 9½ years of age, got sand in her eye in November, 1952. Because of this trivial injury she was seen by an ophthalmologist, who discovered a lightly pigmented lesion in the right iris at 6 o'clock. A melanoma was suspected, and wide iridectomy from 4 to 8 o'clock was performed one week after the injury. Examination of the surgical specimen revealed a nonpigmented tumor composed of slender melanoma cells of spindle-A type which infiltrated the stroma and extended along the anterior surface of the iris as a placoid mass. Parts of the tumor presented leiomyoid features.

The patient was well and without recurrence five years after iridectomy.

CASE 3 (A. F. I. P. Acc. 637051).—A white girl, who was 14 years old at the time of iridectomy, had first been seen in 1946 at the age of 6 years, because of right esotropia and compound hyperopic astigmatism. The squint was controlled with glasses. Examination had also revealed a "congenital pear-shaped pupil" in the left eye. The child was examined annually. On Feb. 1, 1954, a whitish-yellow tumor was discovered in the lower outer sector of the left iris, the site of the congenital deformity of the pupil. Gonioscopy revealed that the chamber angle was not involved. A wide basal iridectomy was performed on March 10, 1954. The tumor had become about 25% larger in the six weeks it was under observation. Microscopic examination revealed a nonpigmented locally infiltrative tumor composed of slender, elongated cells of spindle-A type. Parts of the tumor had a distinctly leiomyomatous appearance. Because it seemed to have arisen within a deformed iris at the apex of the congenitally pear-shaped pupil, it is suspected that iris tumors of this type, with features of nevus, spindle-A melanoma, and leiomyoma, may be basically hamartomatous.

TABLE 3.—*Distribution of Cases According to Zone of Iris Involved*

	Cases, No.
Pupillary	30
Pupillary and midzonal	17
Midzonal only	13
Peripheral and midzonal	6
Peripheral	11
Entire sector	23
No information	25
Total	125

The patient has been followed for three years since the iridectomy and has shown no evidence of recurrence.

These three cases have several features in common. In each the patient was between 9 and 14 years of age when the iris tumor was discovered. The tumors, all in the lower or lower outer quadrants, were remarkably similar in microscopic appearance. We considered each to be a nonpigmented melanoma of spindle-A type with leiomyomatous features, probably hamartomatous in nature. In the fourth case, the tumor would seem to be of a different type.

CASE 4 (A. F. I. P. Acc. 605784).—In May or June, 1953, a 4-year-old white boy was first observed to have a heavily pigmented tumor near the pupillary margin of the upper temporal quadrant. The mass increased in size and was removed at iridectomy on Aug. 8, 1953.

Microscopic examination revealed an infiltrative tumor composed of pigmented spindle-shaped cells presenting features of both the Callender A and B types. Unfortunately, we have been unable to obtain follow-up data in this unusual case.

Sex and Race.—Of the 125 patients in this series, 70 were male and 55 were female. Differences in age distribution between males and females were not significant (Fig. 1). This is true also of patients with melanomas of the ciliary body and choroid. The observation that malignant melanomas of the uvea, like those of the skin, are rarely seen in nonwhite persons applies also to iris tumors, for only 2 of the 125 patients in this series were Negroes.

Location of Tumors.—The right eye was affected in 51 patients; the left eye, in 62, and this information is not available for the remaining 12. In view of the fact that this study was based entirely on tumors treated initially by iridectomy, it is not surprising that the greater number were limited to the pupillary and midzonal regions (Table 3). Tumors of the peripheral iris tend to involve the ciliary body and outflow channels

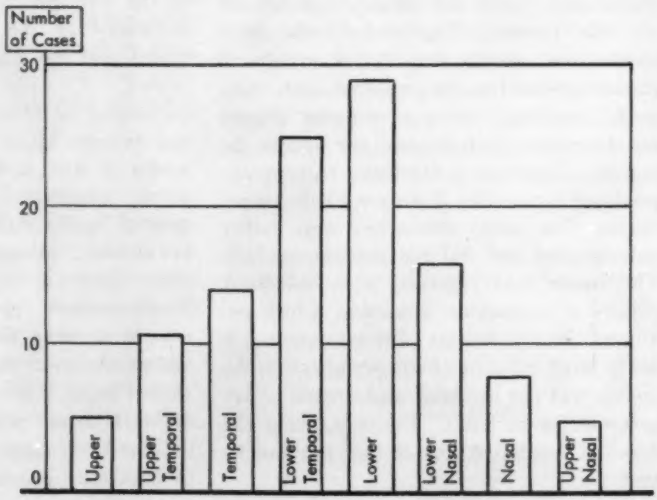

Fig. 2.—Distribution of cases according to sector of iris involved.

TABLE 4.—*Distribution of Tumors Unrecognized By Patient, by Sector of Iris Involved*

Sector Involved	Total Cases	Unrecognized *
Upper	5	3
Upper temporal	12	4
Temporal	14	5
Lower temporal	25	10
Lower	29	8
Lower nasal	16	5
Nasal	8	1
Upper nasal	5	1
Total	114	37

* Tumor discovered in course of routine examination.

earlier, and therefore, even though small and localized, they are often treated by enucleation.

Information on the position of tumors on the iris in respect to the sector involved is available in 113 cases. The data from these have been plotted in the form of a frequency distribution curve (Fig. 2). A striking concentration of cases is evident in the lower and lower temporal sectors, regardless of the eye involved. From these sectors the concentration of cases falls off sharply both nasally and temporally, sectors 180 degrees away showing the lowest concentration (Fig. 2). The biologic significance of this observation remains obscure. The lower half of the iris receives a greater exposure to sunlight, but since tumors discovered early in childhood are as likely to involve the lower iris as are those detected in later life, we doubt that the degree or duration of exposure could account for this distribution. The data also provide no basis for assuming that tumors in the upper and upper nasal quadrant are more likely to escape the patient's attention, for tumors discovered in the course of routine examination have the same distribution as those known to be of long duration (Table 4).

Clinical Appearance of Tumors.—The tumors varied considerably in size, shape, and degree of pigmentation. The outline of 26 tumors was round; of 16, oval; of 14, irregular; of 4, wedge-shaped; of 3, racemose, and of 62, not specified. Thirty-four were described as elevated, and only two were said not to be elevated; the remainder were not described in this respect. In 74 cases the iris adjacent to the tumor was not involved, but in 18 the melanoma lay against or infiltrated adjacent structures: the chamber angle in 9, the iris root in 2, the cornea in 3, the lens in 3, and diffusely in 1. The extent of involvement was not described in 33 cases. Pigmentation of the melanoma was heavy in 11, moderate in 21, medium in 18, light in 10, absent in 3, and not described in 62. Heterochromia was recorded in nine cases (Table 5). Abnormal blood vessels supplying the tumors were said to be present in 25 cases, not present in 47, and were not mentioned in 53. Hemorrhage into the anterior chamber was known to have occurred in 13 cases (Table 6). Some type of deformity of the pupillary outline was demonstrable in at least 52 cases, and ectropion of the pupil was noted in 31.

A change in the appearance of the iris tumor was described in only 69 cases (Table 5), but this is not surprising, since it will be recalled from Table 2 that in only 67 cases was the tumor the patient's chief complaint. The change most frequently described was an increase in size; less often, a change in size and color, and rarely, a change in color only.

Glaucoma.—In six patients the tumor-bearing eye was glaucomatous at the time

TABLE 5.—*Change in Appearance of Tumor* *

	Cases, No.
Enlargement	58
Increased pigmentation	4
Change in size and color	8
No change	23
No information	32
Total	125

* Heterochromia iridis was noted in nine cases.

TABLE 6.—*Other Abnormalities Observed*

	Cases, No.
Deformity of pupil	52
Ectropion of pupil	31
Abnormal vascularity	25
History of hyphema	13
Glaucoma	11 *

* In five of these cases glaucoma occurred only after recurrence of tumor.

TABLE 7.—*Initial Operation*

	Cases, No.
Diagnostic iridectomy	27
Excisional iridectomy	95
Cataract extraction and iridectomy	2
Iridencleisis and iridectomy	1
Total	125

TABLE 8.—*Operations Subsequent to Iridectomy*

	Cases, No.
None	75
Early reexcision of iris	1
Early enucleation	38
Enucleation after recurrence	5
Iridectomy and enucleation after recurrence	1
No information	5
Total	125

of iridectomy (Table 6). In five of these the glaucoma was believed to be the result of invasion of the outflow pathways by the neoplasm. The sixth patient was believed to have an unrelated primary glaucoma. In an additional five patients glaucoma developed when the tumor recurred after iridectomy.

Surgical Management.—All of the 125 patients were treated initially by iridectomy (this was a principal criterion for selection of cases). In three instances, however, iridectomy was not the primary objective (Table 7). In one case a biopsy specimen of another sector of iris was obtained during iridencleisis; in two others iridectomy was incidental to cataract extraction. Iridectomy was undertaken with the intention that it would represent a definitive excisional procedure in 95 cases and as a means of pathologic diagnosis in the remaining 27.

After the pathologist reported "malignant melanoma," the surgeon elected to enucleate the eye immediately in 38 cases (Table 8). In 27 cases this decision was based on the assumption or knowledge that the tumor had not been completely removed (Table 9). We have good reason to believe that in 11 cases enucleation was performed simply because of the diagnosis of malignant melanoma (Table 9). Seven of these operations have been performed since Jan. 1, 1952, which suggests an increasing tendency to enucleate when iridectomy alone would have sufficed (Table 10). A similar observation was made by Duke and Dunn.[2]

TABLE 9.—*Reasons for Enucleation*

	Cases, No.
Incomplete excision of tumor	27
Recurrence of tumor	6
Histopathologic diagnosis of malignant melanoma	11
Total	44

In one case in which all of the tumor had not been removed at iridectomy, enucleation was recommended but refused by the patient. The residual tumor was then excised by a second iridectomy. This patient is living and free of recurrence seven years later.

Enucleation was necessary in six cases because of recurrent tumors which had led to secondary glaucoma. There remain 73 cases in which the initial iridectomy has been the only surgical procedure employed.

Follow-Up.—All but 6 patients have been followed (Table 11), and only 14 have

TABLE 10.—*Justified Versus Unjustified Early Enucleation Related to the Periods "1951 and Earlier" and "1952 and Later"* *

	No.			Per Cent			Significance		
Period	Justified	Unjustified	Total	Justified	Unjustified	Total	χ^2	Degrees of Freedom	Level of Probability
Before 1952	19	4	23	82.6	17.4	100.0	2.494 †	1	0.13
Since 1952	8	7	15	53.3	46.7	100.0			
Total	27	11	38	71.0	29.0				

* Interpretation: A χ^2-test, based on the distribution of "unjustified" early enucleations in the 23 patients treated prior to 1952 and 15 who were treated during and after 1952, revealed that the odds are slightly less than 7:1 that a tendency has developed in the later period to enucleate soon after iridectomy as a matter of caution when the pathologic diagnosis is malignant melanoma.

† Yates' adjustment was applied because of the smallness of frequency (4) for "unjustified, before 1952."

TABLE 11.—*Follow-Up*

	Cases, No.
No information	6
"Tumor deaths"	3
Dead of other causes	11
Living with metastasis	1
Living, free of tumor	104
0–5 yr.	37
5–10 yr.	34
10–15 yr.	23
15–37 yr.	10

died. Eleven deaths were attributable to other causes (Table 12). Three of the patients were believed to have died of metastasis, but in none of these cases was an autopsy performed. It is apparent from the actuarial data presented in Table 13 and Figure 3 that the patients in this series are likely to die of causes unrelated to the iris tumors.

Abstracts of the three "tumor deaths" follow.

CASE 5 (A. F. I. P. Acc. 29886).—A white woman noticed a small pink spot on her right iris in 1922, when she was 30 years of age. The lesion slowly increased in size. When she was first examined, in 1927, a pinkish-yellow tumor involved the lower temporal quadrant and pressed against the cornea. The intraocular pressure was 60 mm., and the disc was cupped. Visual acuity was 15/40. The eye was otherwise normal. Wide iridectomy was performed in April, 1927. Microscopically the resected tumor was highly cellular,

TABLE 12.—*Length of Survival and Causes of Death Among Thirteen Nonsurvivors*

A. F. I. P. Acc. No.	Survival After Iridectomy	Causes of Death	
		Clinical	Autopsy
29886	10 yr.	Metastasis from malig. melanoma of iris	None
39802	2½ yr.	Drowned	None
56294	5½ yr.	Metastasis from malig. melanoma of iris	None
66511	9½ yr.	------	Generalized arteriosclerosis with coronary heart disease
73426	9¼ yr.	"Stroke"	None
146090	11 yr.	Mediastinal tumor	Primary malignant tumor of mediastinum
181694	7 wk.	"Heart attack"	None
182466	4½ yr.	Diabetic acidosis	Atrophy of pancreas, pulmonary edema, generalized arteriosclerosis
202657	9 yr.	Cerebral hemorrhage	None
237339	1 yr.	Metastasis from malig. melanoma of iris	None
239361	5½ yr.	------	Adhesive & constrictive pericarditis; coronary heart disease
265045	5 yr.	"Not from metastasis"	None
589503	3 yr.	Cerebral vascular accident	None
693428	3 yr.	Carcinoma of stomach with diffuse peritoneal spread	None

TABLE 13.—*Tumors of the Iris Treated Initially by Iridectomy—Actuarial Survival Rates for Seventy-Two Cases*

Interval from Initial Surgery to Last Known Status, Yr.	Last Known Status				Alive At the Beginning of the Interval, No.	Actuarial Survival Rates				
	Dead			Alive		Person-Yr. Exposed to the Probability of Dying	Based on Deaths from All Causes		Based on Deaths with Tumor Only	
	With Tumor	Other & Unknown Causes	Total				Probability of Dying in the Interval	Per Cent Survival (to x Interval)	Probability of Dying in the Interval	Per Cent Survival (to x Interval)
0– 1	0	1	1	0	72	72.0	0.0139	100.0	*	100.0
1– 2	1	0	1	0	71	71.0	0.0141	98.6	0.0141	100.0
2– 3	0	1	1	0	70	70.0	0.0143	97.2	*	98.6
3– 4	0	0	0	0	69	69.0	*	95.8	*	98.6
4– 5	0	1	1	0	69	69.0	0.0145	95.8	*	98.6
5– 6	0	2	2	11	68	62.5	0.0320	94.4	*	98.6
6– 7	1	0	1	6	55	52.0	0.0192	91.4	0.0192	98.6
7– 8	0	0	0	6	48	45.0	*	89.7	*	96.7
8– 9	0	0	0	4	42	40.0	*	89.7	*	96.7
9–10	1	2	3	3	38	36.5	0.0822	89.7	0.0274	96.7
10–11	0	0	0	10	32	27.0	*	82.3	*	94.1
11–12	0	1	1	3	22	20.5	0.0488	82.3	*	94.1
12–13	0	0	0	5	18	15.5	*	78.3	*	94.1
13–14	0	0	0	3	13	11.5	*	78.3	*	94.1
14–15	0	0	0	3	10	8.5	*	78.3	*	94.1
15 and over	0	0	0	7	7	—	—	78.3	—	94.1

* No deaths occurred during the interval.

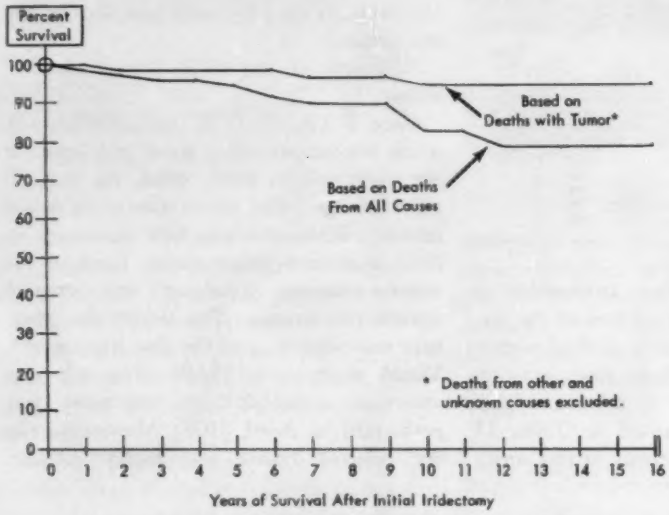

Fig. 3.—Actuarial survival rates for 72 cases of tumors of the iris initially treated by iridectomy prior to 1953.

composed of tightly packed, virtually nonpigmented, cells of both spindle and small epithelioid varieties.

On examination in October, 1927, the eye was in good condition and the tension had dropped to 22 mm. Visual acuity was 15/30. In the lower nasal quadrant the iris appeared thickened and seemed to be pressing against the peripheral cornea. The patient refused enucleation. In November, 1928, she returned because of a red swelling beneath the conjunctiva just above the cornea. The lesion measured 8×6 mm., and its long axis was horizontal. The recurrent tumor in the inferior nasal angle had extended to involve a fourth of the circumference of the chamber angle. The eye was enucleated on Nov. 14, 1928.

Microscopic examination revealed diffuse thickening of the entire iris, which was densely infiltrated by lightly pigmented melanoma cells of spindle-B type. The tumor replaced the iris stroma and extended posteriorly through the pigment epithelium, laterally into the ciliary body, and forward into the anterior chamber angle and canal of Schlemm. Episcleral tumor nodules were present at the limbus on both sides in the plane of section. There was deep glaucomatous excavation of the optic disc.

The patient remained in good health for six years after enucleation. In April, 1935, a metastatic lesion of the rib was resected. Metastasis became widespread, and the patient died in March, 1937. Autopsy was not performed, and to date we have been unable to obtain sections of the rib metastasis for confirmation of the diagnosis of metastatic malignant melanoma.

Case 6 (A. F. I. P. Acc. 56294).—A 48-year-old white woman noticed a spot on her right iris about a year before her first examination in December, 1934, when the spot seemed to have grown larger and the vision in that eye seemed to have become blurred. Examination revealed a dark-brown tumor, 6 mm. in diameter, on the temporal side of the iris, extending from the pupillary margin to the ciliary body. The patient elected wide iridectomy rather than enucleation. This procedure was carried out on Dec. 15, 1934. The postoperative coloboma involved an arc of 150 degrees on the temporal side.

Microscopically, thickening of the iris had resulted from diffuse infiltration by moderately pigmented plump spindle-

shaped cells. Also present were larger cells with scanty cytoplasm and many deeply pigmented cells with elongated dendritic processes. The tumor had not only broken through the anterior surface of the iris, but had also broken through the dilator muscle and pigment epithelium posteriorly.

In June, 1935, several pigmented spots appeared in the nasal conjunctiva. A flat segment of perilimbal conjunctiva and peripheral cornea was resected. It measured 7×4×1 mm. and contained three small pigmented spots. Recurrent malignant melanoma was the pathologic diagnosis. In November the intraocular tension rose to 60 mm. (McLean), and, since there was further evidence of recurrent melanoma, the eye was enucleated on Dec. 8, 1935. Histopathologic study of the eye confirmed the diagnosis of recurrent malignant melanoma of the iris, mainly at the iris root, with infiltration of the anterior chamber angle and along the emissaria into the episcleral and conjunctival tissues. The tumor was very cellular, but mitotic figures were rare. Nuclei of tumor cells were densely packed, and the cytoplasm, scant.

Small recurrent pigmented tumors were excised from the conjunctiva of the socket in December, 1937, and again in July, 1939. Then a submandibular metastasis appeared and the patient presented symptoms indicative of liver metastasis. The patient died in June, 1940, five and one-half years after iridectomy. Autopsy was not performed.

Case 7 (A. F. I. P. Acc. 237339).—A 70-year-old white man was seen because of a pigmented tumor of the lower nasal quadrant of the right iris. It had been present for many years but recently had seemed to be enlarging. Although it was suspected that the tumor extended into the ciliary body, iridectomy was performed on Jan. 21, 1949.

Microscopically, the iris tumor was very vascular, hemorrhagic, and moderately pigmented and was composed of a mixture of spindle-A, spindle-B, and epithelioid cells. Because the tumor was believed to have been incompletely excised, enucleation was performed one week later. On histopathologic examination, clumps of residual tumor were seen in the corneal wound and on the anterior surface of the remaining iris. The patient died in February, 1950. Autopsy was not performed, but the clinical impression was that metastasis was the cause of death.

Two of these fatal cases (A. F. I. P. Acc. 29886 and 56294) are among the six in which enucleation was performed because of delayed recurrences following iridectomy. The four nonfatal cases of delayed recurrence are abstracted as follows.

Case 8 (A. F. I. P. Acc. 70076).—A 43-year-old white man, whose right eye was enucleated in August, 1940, gave the following history. In 1920 a small tumor was noted at the lower edge of the iris. In 1937 this tumor began to spread over the iris and surgical excision was attempted. The pathologic diagnosis was melanotic sarcoma. The tumor recurred in 1939, and the eye, which was almost blind from cataract and glaucoma, was enucleated. Microscopically, recurrent growth of plump pigmented spindle cells of Types A and B were seen in the iris root and anterior chamber angle. Much of the angle, however, was occluded by anterior synechiae rather than tumor cells.

The patient was still living and without evidence of metastasis 16½ years after iridectomy and 37 years after the tumor was first observed.

Case 9 (A. F. I. P. Acc. 95390).*—A 23-year-old white man first noticed in June, 1943, that his right pupil was irregular. A somewhat papillomatous yellow-brown tumor was seen near the pupillary margin in the upper temporal quadrant of the right eye. Iridectomy for excision of the tumor was performed on July 7, 1943. The original pathologic diagnosis was leiomyoma.

Ten years later the patient noticed a "brown spot on the right eye." Examina-

* This case was reported previously by us.[5]

tion revealed a brownish subconjunctival tumor at the site of the original iridectomy and another brownish tumor of the iris, which extended into the angle at the lower nasal quadrant. The latter was removed by iridectomy on April 16, 1954, but the scleral tumor was not excised. By January, 1955, the visual acuity of the right eye was reduced to 20/400, correctible to 20/80. Recurrences were observed on the iris and at several points in the angle, but the epibulbar nodule remained unchanged. Radioactive phosphorus uptake was not increased. The eye was enucleated. Histopathologic examination revealed intraocular recurrence and episcleral extension of a very lightly pigmented malignant melanoma of spindle-A type. Review of the original iridectomy specimen showed that it was of similar cell type, although virtually all cells were amelanotic.

The patient was in good general health 3 years after enucleation, almost 15 years after the initial iridectomy.

CASE 10 (A. F. I. P. Acc. 327763).†—A 45-year-old white man observed that his left pupil had become progressively more irregular over a period of a year. Examination revealed a pigmented lesion covering part of the upper temporal sector of the iris. It was in this same area that the pupil was deformed, and here the iris was adherent to the lens. Scattered pigment was observed on the lens and iris. Iridectomy was performed on Feb. 14, 1951, and a pathologic diagnosis of malignant melanoma of the iris was established.

Four years after iridectomy the eye became painful. Administration of physostigmine (eserine) and pilocarpine did not relieve the pain. The results of radioactive phosphorus studies were within normal limits. In the course of the next few months visual acuity was reduced to 20/60 (corrected). Unusually heavy pigmentation was observed in the angle and on the lens, but a definite tumor was not seen. Much of the iris appeared atrophic, and the disc was cupped. The eye was enucleated on Aug. 6, 1955. Microscopically, the anterior chamber angles were diffusely infiltrated by recurrent melanoma cells, which filled the intertrabecular spaces and canal of Schlemm. Predominating in the infiltration of the iris root and adjacent ciliary body was a large epithelioid cell.

The patient has been followed for only one year since enucleation.

CASE 11 (A. F. I. P. Acc. 749919).—A white woman was first seen in December, 1941, because of an iris lesion known to have been present for 10 years. It had appeared after the patient had been struck in the eye by a foreign body. For five years the eye was quiescent, but during the ensuing five years repeated transient hyphemas occurred. Finally the lesion encroached sufficiently upon the pupillary aperture to interfere with vision. Examination revealed a mass on the lower nasal quadrant of the iris of the right eye, which extended from the periphery into the pupillary space. The mass, which measured 5×7 mm., was translucent, nonpigmented, and papillomatous. It was covered by prominent bleb-like blood vessels. The morning after examination another spontaneous hyphema occurred. Iridectomy was performed on Jan. 22, 1942. Postoperatively, visual acuity was 6/60 (uncorrected).

The patient was lost to follow-up for several years. Meanwhile, she had moved to another part of the country. The visual acuity of her right eye gradually declined, and eight years after iridectomy all light perception was lost. In September, 1955, the eye became very painful. It was injected and the tension was above 70 mm. Hg. The cornea was fairly clear, and the iris coloboma could be visualized. Although evidence of recurrent tumor was not found, the eye was enucleated because it was blind and painful. Histopathologic examination of the enucleated eye revealed recurrent tumor in the anterior chamber angle. The neoplasm was composed of virtually amela-

† This case was reported previously by us.[5]

notic cells of spindle-A type which had invaded the trabecula. Sections from the iridectomy specimen, obtained for comparison, showed that the original tumor was composed of identical cells. When last seen the patient was in good general health and without evidence of metastasis.

Histopathology.—An attempt has been made to classify these iris tumors according to Callender's three main cell types: spindle-A, spindle-B, and epithelioid.[6] Cells of spindle-A type are slender and elongated and contain an equally slender and elongated nucleus in which the chromatin is rather evenly dispersed or sometimes lined up along the central axis. Nucleoli are characteristically absent. Spindle-B cells are larger, with more abundant cytoplasm and more ovoid nuclei. Greater variations in the content and distribution of chromatin are observed in the nuclei; nucleoli are typically present, though not always large or prominent. Spindle-B cells cover a broad spectrum, merging with spindle-A cells at one end and epithelioid cells at the other. Epithelioid cells are of various shapes, but they contain so much cytoplasm that they no longer appear as spindle cells. They are the most pleomorphic of all the melanoma cells. Multinucleated giant cells are often associated with them. Their nuclei are generally large, and the nucleoli are conspicuous. There are also various combinations of spindle and epithelioid cells; tumors of this composition are known as "mixed-cell type."

In the posterior uvea the commonest melanoma is the mixed-cell type; next in frequency is the spindle-B type. In the iris, all cell types found in choroidal tumors may be encountered, but their relative frequency is different. The majority of iris tumors are composed of cells of very benign appearance. Tumors composed purely of small spindle-A and nevus-type cells, while uncommon in the posterior uvea, are the commonest in the iris. Even when there is an admixture of spindle-B and epithelioid cells, in iris tumors these are seldom conspicuous constituents of the cell population.

Tumors of the iris present a problem rarely encountered in those of the posterior uvea. Because tumors do arise from the involuntary muscles of the iris, and because these muscles are also partially pigmented neurectodermal derivatives, differential diagnosis between leiomyomas and nevi and melanomas may be difficult. Our study has suggested that there is no sharp clinical or pathologic distinction between these two seemingly different groups of tumors.

A more detailed description and discussion of the cytology and histogenesis of iris tumors will be given in another paper. For our purpose here it will suffice to divide the cases into two broad groups according to the cytologic characteristics of the tumors. The larger, Group I (87 cases), includes all tumors of the nevus-melanoma and leiomyoma types with cytologic features considered typical of "benign cells," incapable of distant metastasis. In spite of their inert appearance, however, these cells are infiltrative; they may invade the anterior chamber angle, ciliary body, and outflow channels. Occasionally, they are dispersed by the aqueous and seed into the angle or onto other portions of the iris. For these reasons, we believe there is no sharp division between "benign" and "malignant" tumors of the iris. In Group II (38 cases) we have placed those tumors which contain cells believed capable of metastasis. But here, again, we cannot prognosticate, on the basis of cytology alone, which tumors will metastasize and which will not, since only three tumors in this series are believed to have produced distant metastasis.

Obviously, with so few "tumor deaths" we have had little opportunity in this study to learn which cytologic features are suggestive of a poor prognosis. It is noteworthy, however, that the three patients whose deaths are believed to have resulted from metastasis had iris tumors which cytologically belonged in Group II. But for each of these tumors that metastasized

there were 12 others in Group II that did not! Hence, if we can draw any conclusion from this study, it is this: Regardless of the histologic appearance of an iris tumor, if it is small enough to be removed by iridectomy the prognosis is excellent (Table 13, Fig. 3). If the tumor has not been excised completely, there is a distinct possibility that it will recur and that ultimately the eye will have to be enucleated because of recurrence or secondary glaucoma. Even with such a delayed intraocular recurrence, however, the prognosis is relatively good, for distant metastasis has occurred in only two of six such cases.

The case material studied has not been sufficient for evaluation of the prognostic significance of the reticular fiber content as determined by Wilder's stain[7] in posterior uveal melanomas.[8] Furthermore, it has been observed that even in the very benign-appearing tumors of nevoid and spindle-A type, the part of the tumor which grows along the anterior surface of the iris is often without reticular fibers.

Comment

Our observations to date, based on the studies reported here and on those of diffuse malignant melanomas of the iris,[5,10] have convinced us of the relative benignity of iris tumors, a conclusion which many other workers in the field have also reached. Documentation with statistical data based on sizable series of cases with long follow-up histories has, however, been conspicuously lacking. Stallard,[11] for example, made the following statements:

> The prognosis after adequate and careful surgical removal of malignant melanoma of the iris is good, for such neoplasms are commonly slow growing, and a feature of their morbid histology which substantiates this fact is the absence of karyokinetic figures. They are composed of spindle cells, a cytological type which, together with a rich argentophil reticulum, in the case of malignant melanomata of the choroid, has a better prognosis than other cellular varieties.

Although he furnished no evidence to support these significant statements, Stallard[11] goes on to even more remarkable expressions concerning the surgical management of iris tumors:

> Neoplastic infiltration of the posterior surface of the cornea and of the structures at the filtration angle including the base of the ciliary body used to be considered a contraindication to the local removal of a malignant melanoma by iridectomy; however, although these neoplastic extensions are undesirable they are not insuperable barriers to effective surgical extirpation, for it is possible with a trephine of appropriate size to remove in some cases the affected part of the cornea with an adequate surround of normal cornea and to replace this with a corneal graft. When the periphery of the neoplasm has reached the filtration angle and it is suspected that only a thin sheet of cells may have infiltrated the base of the ciliary body, surface diathermy has been successful in their destruction.

Although we have had no personal experience with such daring attempts at excisional surgery of iris tumors which have infiltrated the trabecula and ciliary body, we do believe that our histopathologic and follow-up studies furnish support for Stallard's contentions. His advice deserves consideration.

Conclusions

Primary tumors of the iris present important differences in their histogenesis, clinical features, surgical management, and natural behavior which justify their being segregated from tumors of the posterior uveal tract.

Two-thirds of iris tumors which are sufficiently small and discrete to be removed by iridectomy are composed of benign-appearing nevus, leiomyoma, and spindle-A-type melanoma cells. These tumors may be infiltrative and locally destructive, but they probably never metastasize. The remaining third of these tumors contain spindle-B and epithelioid cells, which often appear as relatively inconspicuous elements within a tumor basically of nevoid or spindle-A type. Of the 38 such tumors in this study, only 3 are believed to have metastasized.

Tumors that are well demarcated, particularly those in the pupillary and midzonal portions of the iris, need not be treated at all unless they have shown evi-

dence of growth or have produced local disturbances, such as hyphema, pupillary obstruction, or cataract. Those located at the periphery should be excised early, for, if they begin to grow, extension into the ciliary body and anterior chamber angle is likely.

Enucleation is probably never justified simply because the pathologic diagnosis of an iridectomy specimen is "malignant melanoma." Evidence of incomplete excision with residual tumor in the ciliary body or anterior chamber angle is a legitimate reason for enucleation.

Conservatism is recommended in the management of iris tumors, because, with rare exceptions, they do not affect the patient's life expectancy.

The many contributors to the Registry of Ophthalmic Pathology furnished clinical data and follow-up histories. Miss E. V. Paul has for a number of years kept an orderly file of all iris tumors in the Registry of Ophthalmic Pathology. Mrs. E. C. Espeut was instrumental in obtaining the large number of good follow-up histories. Mr. B. L. Parnell performed the statistical analyses with the assistance of Miss M. Fraker, who also abstracted and compiled the data. Mrs. H. K. Steward gave editorial assistance.

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The Adaptation of Virac, a New Iodophore, to Clinical Use

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The germicidal properties of iodine are well known. Indeed, it has been used with good results as an antiseptic for many decades. Its merits for this purpose, recently reviewed by Gershenfeld,[1] are numerous. First, it is bactericidal rather than bacteriostatic. Second, such action is rapid and is achieved in comparatively low concentration. Third, unlike most germicides, iodine is essentially equipotent against all bacteria. Fourth, in addition to its bactericidal properties, iodine has well-known activity against spores, fungi, and viruses. Fifth, its tissue toxicity is comparatively low, the toxicity index being less than that of benzalkonium chloride, mercuric chloride, or phenol.[1]

In spite of its potency and widespread use as a home remedy, iodine finds only limited application in clinical medicine. Most commonly iodine has been used as a skin disinfectant prior to surgery. There is little doubt of its value for this purpose.[2,3] However, the use of iodine as a skin disinfectant has certain disadvantages. It stains the skin and is rather caustic. In addition, a fairly high incidence of sensitivity to iodine, around 15%, is encountered.[2]

In similar dilutions iodine is generally more irritating to mucous membranes than to skin, owing no doubt to its caustic action. Often, however, the distinction between irritation and true toxicity must be kept in mind. Thus it has been determined that concentrations of iodine in excess of 0.025% are irritating to the eye.[4] On the other hand, 2% tincture of iodine is often used for denudation of the cornea in cases of herpetic keratitis, with no permanent toxic effect.

Some of the objectionable properties of iodine have been removed by the preparation of so-called iodophores, or iodine carriers. These are water-soluble mixtures of elemental iodine and an organic carrier. A loose linkage forms between the two, an equilibrium between the complex and dissolved iodine being obtained. Iodine is presumably released from the complex as it is utilized from solution.

Recently a new iodophore, a complex of elemental iodine and a quaternary ammonium base (N-methylheptylcolaminoformylmethyl pyridinium chloride) known as Ruson has been made available. The latter is a strong detergent and has, therefore, germicidal activity in its own right similar to but reportedly superior to that possessed by benzalkonium chloride (Zephiran). The combination has been given the trade name Virac. The product has the advantages of providing an iodine preparation which does not stain the skin, has a low iodine vapor pressure, and is not caustic. It is possible but not proved that the combination would allow a greater penetration of the iodine than obtained with other solutions.

The studies with Virac thus far have indicated the product to be an efficient germicide and to have clinical usefulness. Testing its effectiveness as a surgical scrub, Frisch, Davies, and Krippaehne found Virac to be significantly superior as a degerming agent of the skin to a liquid surgical soap (Septisol), hexachlorophene (pHisoHex), and benzalkonium chloride.[5] The same authors found the product to have the wide

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spectrum of germicidal activity expected of iodine, showing activity against a variety of bacteria, certain yeasts, and viruses in dilutions containing 100 p. p. m. of available iodine.

Krippaehne and Frisch[6] further showed that Virac significantly reduced the incidence of postoperative infection when employed as a surgical preparation in general surgical and orthopedic cases, comparison being made with the previously employed Septisol or a liquid soap containing hexachlorophene (Germa Medica) with final benzalkonium chloride wash. The effectivity of Virac as a scrub for the surgeon was also confirmed. In addition, the compound was found of value in a variety of superficial infections, including infected wounds and furunculosis. The effectivity of Virac as a bactericidal agent against antibiotic-resistant Micrococcus pyogenes var. aureus has been reported.[7] These studies have demonstrated Virac to be generally superior to other disinfectants, including benzalkonium chloride.

The toxicity of Virac to the normal skin appears to be low. In patch testing of 155 young adults a skin sensitivity to the product accountable to iodine occurred in only one person.[6] Similar experience was obtained during clinical use. No systemic reactions from topical use were reported. In addition, the product appears to be of low toxicity when ingested by experimental animals.

The successful use of Virac elsewhere suggested its possible adaptation for certain areas about the eye. In particular, it was felt the compound might be of merit as a surgical preparation and as an irrigant for the conjunctival sac and lacrimal apparatus. In addition, the possible value of the compound in the treatment of external diseases was considered. Preparatory to such studies, adaptation of the agent for ocular use and knowledge of its toxicity were necessary. The present paper is concerned largely with this phase of the investigation. Certain preliminary clinical results are also reported.

Material

Virac was provided by the manufacturer in two concentrations of iodine, 3.2% and 10%. In both instances the concentration of the quaternary base was 14.3%. The products were freely miscible with water in all dilutions. Solutions of the quaternary base, Ruson, have low surface tensions (Table 1). Addition of the iodine to form Virac raises the surface tension a measurable but slight degree. In all concentrations tested the surface tension of Virac or its quaternary base was lower than that obtained with benzalkonium chloride. It is interesting that the surface tension of the Virac solutions remained constant with dilution, whereas the surface tension increased as the benzalkonium chloride was diluted.

Although Virac is a cationic detergent, the pH little influenced the surface tension of the Virac solution (Table 2). The surface tension was much the same at pH 2.0 (citric acid solution) as at pH 8.4 (sodium bicarbonate solution).

Diluents

In the course of the work several diluents were tried in an attempt to provide a vehicle which was isotonic and fairly stable. At the onset it was recognized that elemental iodine fairly rapidly disappears at higher pH levels, with a corresponding re-

TABLE 1.—*Surface Tension and pH of Indicated Dilutions of Various Surfactants*

Dilution of Quaternary Base	Ruson		Virac (3.2% I_2)		Virac (10% I_2)		Benzalkonium Chloride	
	Surface Tension, Dynes/Cm.	pH	Surface Tension, Dynes/Cm.	pH	Surface Tension, Dynes/Cm.	pH	Surface Tension, Dynes/Cm.	pH
1:1000	27.7	5.0	32.8	3.2	33.3	2.9	35.5	6.6
1:3000	26.3	5.1	32.6	3.7	33.1	3.3	35.1	6.2
1:5000	26.3	5.2	32.8	4.0	33.4	3.5	39.5	6.2
1:10,000	26.7	5.2	32.8	4.2	33.1	3.8	49.1	6.0

TABLE 2.—*Surface Tension and pH of Virac Solutions Diluted with Indicated Ingredient to Produce a 1:1000 Concentration of Quaternary Base*

Diluent	Virac (3.2% I_2) Surface Tension, Dynes/Cm.	pH	Virac (10% I_2) Surface Tension, Dynes/Cm.	pH
3% citric acid	33.0	2.0	33.5	2.0
1.8% boric acid	33.1	3.2	33.3	3.0
1% sodium bicarbonate	33.8	8.2	34.1	8.4

TABLE 3.—*Compatibility and Iodine Stability of Virac Solutions in Indicated Diluent* *

Diluent	Compatibility	pH	Iodine Stability
3% citric acid	Compatible	2.0	Fairly stable
1.7% acetic acid	Compatible	2.6	Fairly stable
Water	Compatible	3.2	Fairly stable
1.8% boric acid	Compatible	3.2	Fairly stable
5% glucose	Compatible	3.2	Fairly stable
1% sodium bicarbonate	Compatible	8.2	Unstable
3% sodium diethylbarbiturate	Compatible	9.7	Unstable
0.9% boric acid and 0.15 M potassium iodide	Incompatible	3.1	....
0.9% sodium chloride	Incompatible	3.2	....
0.15 M monosodium phosphate	Incompatible	4.1	....
Sodium acetate	Incompatible	6.7	....
Sodium citrate	Incompatible	7.1	....
0.1 M disodium phosphate	Incompatible	8.1	....
0.1 M sodium tetraborate decahydrate	Incompatible	9.3	....

* Concentration of quaternary base is 1:1000.

duction in germicidal activity.[1] This proved true of Virac as well. Those solutions of the highest pH were the most unstable (Table 3). It was found impossible to raise the pH much above 3.0 in a clinically useful dilution and achieve a solution of sufficient stability. Even in that pH range, as will be seen, definite iodine loss occurred over a period of time. In addition to lack of stability, there were certain substances which were incompatible with Virac, causing a precipitation of the complex when added to the solution. Notable among these were sodium chloride, sodium phosphate, and potassium iodide. It is apparent from the above work that the diluents coming closest to achieving the objective of providing an isotonic stable solution were isotonic glucose and boric acid. Of the two, we have used the boric acid diluent.

The compatibilities of the boric acid-Virac mixture with methylcellulose and cellulose gum (carboxymethylcellulose) were also tested. We have come to prefer the carboxymethylcellulose for use in our clinics because of the ease of preparation and patient acceptance. However, Virac proved to be incompatible with carboxymethylcellulose, whereas it is readily compatible with methylcellulose.

Anticipating a possible use of Virac as a preservative in ophthalmic solutions, we have determined that in a dilution providing a 1:7500 concentration of quaternary base Virac was compatible with fluorescein, pilocarpine nitrate, and scopolamine hydrobromide but not with atropine sulfate.

Stability

Even at lower pH, solutions of Virac lost iodine strength during a period of several weeks. This was true whether protected from light or not (Table 4). It was noted that the absolute decrease in iodine strength was fairly constant with time and was about the same at the two concentrations tested. Exposure of the solution to metal caused a

TABLE 4.—*Iodine Content of Various Dilutions of Virac (10%) Stored at Room Temperature Under Indicated Conditions* *

Iodine Content, P. P. M.

Solution	Type of Bottle	Days 0	3	5	11	20	27	41
1:3000 of base in 1.8% boric acid	Clear	288	280	263	274	266	259	252
	Brown	288	278	276	269	255	258	251
1:3000 of base in water	Clear	291	278	278	276	270	263	252
	Brown	291	282	277	275	263	264	253
1:5000 of base in 1.8% boric acid	Clear	172	158	156	148	149	142	136
	Brown	172	159	154	151	141	141	137
1:5000 of base in water	Clear	167	154	151	143	145	130	136
	Brown	167	154	151	152	150	138	134
1:3000 of base in water	Clear	165	—	—	48 (13 days)	48	23 (30 days)	—
	Brown metal cap	165	—	—	50 (13 days)	49	23 (30 days)	—

* Bottles are glass-stoppered unless otherwise indicated.

fairly rapid loss of iodine strength. This was very apparent in the clinic where irrigation bottles with metal caps were employed.

Toxicity

Toxicity to the rabbit eye was checked both in vivo and in vitro. At the outset it seemed reasonable to suppose that the major toxic effect of the drug would result from its increased surface activity. The toxicity of a high concentration of benzalkonium chloride, particularly to the cornea, is well known.[8] This, plus the widespread use of benzalkonium chloride in the field of ophthalmology, lead us to use it as a basis for comparison with Virac.

In vitro toxicity against the cornea was determined in a manner previously reported.[9] This technique depends on the observed fact that the cornea hydrates when the intact eye is stored in a moist chamber at 0 C. This hydration can be reversed when the cornea is subsequently placed at 37 C for a short period of time. Using this procedure, we have demonstrated that benzalkonium chloride is very toxic to the denuded cornea.[10] When corneas were treated with 1% benzalkonium chloride, corneal hydration increased during refrigeration to a much higher level than was normally observed. Additional hydration occurred when the cornea was subsequently placed at 37 C. When 0.1% benzalkonium chloride was used, the cornea hydrated to only the normal extent during refrigeration but, unlike the untreated cornea, it did not dehydrate during subsequent incubation at 37 C.

With use of this technique, Virac in concentrations of 1% and 0.1% of the quaternary base was tested. When the 1% concentration was used the cornea hydrated excessively during refrigeration (Table 5), but the hydration was not as marked as had been observed with 1% benzalkonium chloride (39 moles of H_2O per 100 gm. of dry weight for Virac, as compared with 60 moles per 100 gm. of dry weight when benzalkonium chloride was used). Dehydration during subsequent incubation at 37 C was nil for both substances. When 0.1% quaternary base in Virac was used, the hydration during refrigeration was that of the otherwise unaltered eye. However, during subsequent incubation at 37 C appreciable dehydration occurred, in sharp contrast to the effect of benzalkonium chloride, which inactivated the dehydration mechanism. The in vitro results indicate, therefore, that Virac is less toxic than benzalkonium chloride.

In vivo studies were conducted on the rabbit with use of both benzalkonium chloride and Virac in comparable quaternary base dilutions. The method of application varied from drops at periodic intervals to pooling of the solution over the cornea and

TABLE 5.—*Effect of Various Dilutions of Virac (3.2% Iodine) on the in Vitro Temperature-Reversible Cation and Water Shift of the Cornea*

Procedure	Eyes, No.	Content			Concentration	
		Water, Moles/100 Gm. Dry Weight	Sodium, mEq/100 Gm. Dry Weight	Potassium, mEq/100 Gm. Dry Weight	Sodium, mEq/1,000 Gm. Water	Potassium, mEq/1,000 Gm. Water
Fresh cornea	93	20.0±1.2 (78.2%)	55.2±4.2	10.5±1.2	153.5±5.5	29.1±3.2
Epithelium intact						
0 C for 40 hr.	30	34.2±1.5 (86.0%)	85.8±5.0	14.9±0.9	138.2±5.8	24.1±1.3
0 C for 40 hr. plus 37 C for 6 hr.	22	21.0±1.8 (79.1%)	58.1±5.4	13.8±1.1	154.3±4.3	35.7±4.7
Epithelium removed with Virac (1% quaternary)						
0 C for 40 hr.	11	37.0±1.6 (86.9%)	85.7±4.2	16.7±1.4	128.6±2.4	24.8±2.3
0 C for 40 hr. plus 37 C for 6 hr.	12	38.4±7.9 (88.0%)	98.1±19.9	17.0±3.0	141.5±5.6	23.8±2.9
Virac (0.1% quaternary)						
0 C for 40 hr.	12	35.6±2.0 (86.5%)	84.0±5.9	14.8±3.0	131.2±6.4	23.1±4.5
0 C for 40 hr. plus 37 C for 6 hr.	12	26.8±3.6 (82.6%)	71.7±9.9	11.8±1.6	150.5±5.8	25.1±5.1

conjunctiva for five minutes. In all instances the eyes were examined by slit-lamp biomicroscopy. The pooling technique produced the severest response.

Virac diluted to contain 0.1% of the base was pooled over intact or partially denuded corneas for five minutes. In both instances the conjunctiva became moderately edematous and inflamed. This reaction largely subsided within a day. The corneas with intact epithelium showed an immediate edema. Rather profuse superficial punctate lesions developed rapidly. These changes persisted for one to two days, but generally the eye appeared normal after three to five days.

The response to the same concentration of Virac was more violent when the cornea was denuded. Hyperemia and edema of the iris was more marked, and protein was observed in the anterior chamber. This persisted for a few days but generally was absent by the fifth day. The cornea became more edematous and irregular than when the epithelium was intact. Early there was some sloughing of epithelium. However, epithelialization recurred by the fifth day, and the eyes were essentially normal at the end of a week.

In sharp contrast, the response to 0.1% benzalkonium chloride was much more marked in every detail. Conjunctival injection and edema, iris hyperemia and edema, protein accumulation in the anterior chamber, edema of the cornea, and epithelial disturbance were all severer and persisted longer. Residual stromal opacities were observed when the cornea with the epithelium intact was bathed with 0.1% benzalkonium chloride. The corneas that had been denuded remained edematous, became vascularized, and developed marked scarring. Figures 1 and 2 show the eyes of rabbits on which similar concentrations of benzalkonium chloride and Virac had been pooled over the denuded cornea 23 days previously. Figures 3 and 4 show the respective microscopic sections. No residual damage was seen to follow application of Virac, whereas considerable permanent changes followed the use of benzalkonium chloride.

Other studies of the toxicity of Virac in various dilutions revealed no situation in which permanent damage resulted. Denuded corneas on which Virac containing a 1:3000 concentration of the quaternary base was dropped every one-half hour for seven hours were well healed and apparently normal by

Fig. 1.—Photograph of rabbit eye taken 23 days after 0.1% benzalkonium chloride was pooled for five minutes over partially denuded cornea and conjunctiva.

Fig. 2.—Photograph of rabbit eye taken 23 days after Virac diluted to contain 0.1% quaternary base was pooled for five minutes over partially denuded cornea and conjunctiva.

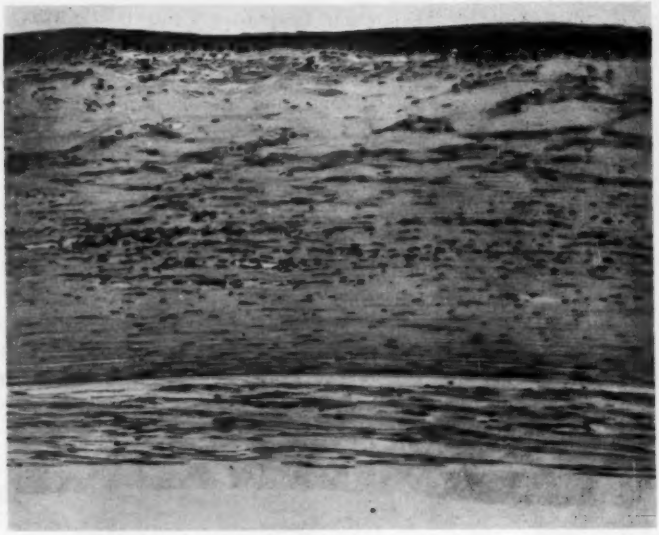

Fig. 3.—Microscopic section of cornea exposed to 0.1% benzalkonium chloride for five minutes (same eye as in Fig. 1); reduced about 13% from mag. × 150.

the next day. Within the concentration limits tested the iodine did not appear to be toxic.

The finding that benzalkonium chloride was much more toxic than Virac poses some interesting questions. It is generally considered that the toxicity of these substances is due to their surface activity. Yet the surface tension at the air-liquid interface was lower for Virac than for benzalkonium chloride. The more reasonable explanation of the discrepancy is that the measurement of surface-tension-lowering effect of a compound is not a true index of its surface activity under other circumstances. The possibility of more specific toxicity must also be considered.

The laboratory results clearly demonstrated that Virac in strongly germicidal concentrations could be used about the eye

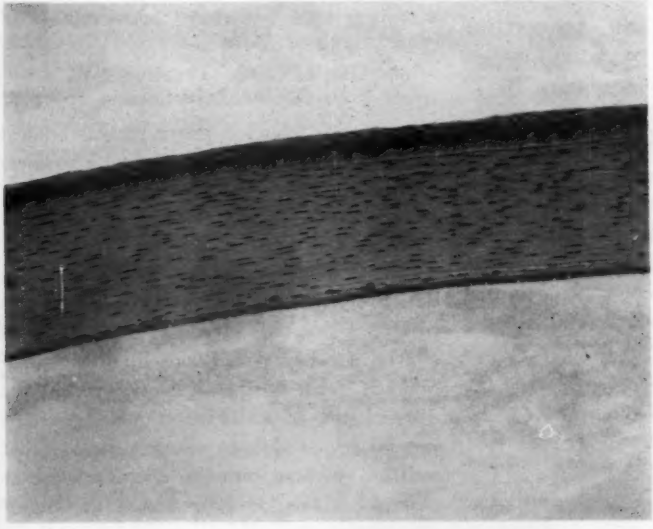

Fig. 4.—Microscopic section of cornea exposed to Virac diluted to contain 0.1% of quaternary base (same eye as in Fig. 2); reduced about 12% from mag. × 150.

with relative safety. From our laboratory studies it was concluded that, while higher concentrations might not be permanently damaging, a maximum concentration of quaternary base of 1:3000 should be applied to the conjunctival sac. This concentration, containing a calculated 230 p. p. m. of iodine is, however, a potent germicidal product,[6,7] superior to and less toxic than a similar concentration of benzalkonium chloride.

Use of Virac as a Surgical Preparation for Ocular Surgery

Virac solutions have been used exclusively as a surgical preparation prior to ocular surgery at the University of Oregon Medical School Hospital and Clinic and the Portland Veterans' Administration Hospital since October, 1957. A 1:10 dilution of stock Virac (3.2% iodine before dilution) was utilized. The preparation technique was the same as had been previously employed with hexachlorophene. The face and lids were scrubbed for about 10 minutes, after which the excess was removed with a dry sponge. (Virac is not intended to be and should not be used as a paint.) The Virac left a faint yellow stain on the prepared skin. This lasted a few hours.

No cases of skin or conjunctival irritation were observed in this series of approximately 200 cases.* No postoperative infections were encountered in the cases in which this preparation was used.

Use of Virac as an Ocular Irrigant

Virac solutions have been used exclusively as an irrigant of the conjunctival sac and lacrimal apparatus in the department of ophthalmology at the University of Oregon Medical School since October, 1957, replacing the previously employed 1:7500 dilution of benzalkonium chloride in isotonic saline. For this purpose a 1:5000 dilution of the quaternary ammonium base in boric acid was prepared. The iodine concentration as determined by titration was approximately 170 p. p. m. A boric acid concentration of 1.8% provides a solution essentially isosmotic with tears. The osmotic pressure of Virac diluted with 1.8% boric acid was 302 mOsm. per liter. The final pH and surface tension were as indicated in Table 2. This solution tended to plug the narrow aperture of some of the irrigation bottles as it dried on the tip. To circumvent this, the concentration of boric acid was reduced to 0.9% in some instances. The two concentrations were equally well tolerated.

Patient acceptance of the irrigant (involving at least 35 irrigations per day in as many different persons) has been good. In general, no corneal disturbance was produced. An occasional moderate hyperemia of the conjunctiva developed, but this lasted only a short time. A few persons complained of irritation which lasted for a few minutes. Irrigation of the lacrimal apparatus was equally well tolerated. (The material can be swallowed with no danger.) We cannot state at the moment that the product aids in the clearing of dacryocystitis. Certainly, it appears to be a superior irrigant to benzalkonium chloride, being less toxic and possessing greater germicidal activity.

Use of Virac Treatment of Ocular Infections

It was the original intent of our clinical studies to evaluate the product as a surgical preparation and as an irrigant. As corollary studies, however, adaptation of the product as a possible adjuvant in the treatment of certain ocular infections, particularly those due to viruses and antibiotic-resistant M. pyogenes, seemed advisable. There is, of course, a fairly voluminous literature, particularly from the preantibiotic era, on the use of iodine in ocular infections. This need not be reviewed here except to state that uniform success with the agent was never obtained. It is recognized that the major

*A surgical nurse who accidentally splashed this solution in her eye showed no corneal lesion or other evidence of irritation when examined one-half hour afterward. However, contact of this dilution with the conjunctiva should be avoided. When it occurs, immediate irrigation is indicated.

limitations of iodine for the treatment of ocular infections are its rapid inactivation by organic matter, its poor penetration, and its caustic nature. While the latter limitation does not apply to the Virac solutions here employed, the former two are very significant.

As patient-administered drops we have employed Virac diluted in a solution containing 1.8% boric acid and 0.75% methylcellulose in concentrations of 1:3000 or 1:5000 of the quaternary base. These contained, respectively, approximately 270 and 170 p. p. m. of iodine as determined by titration.† In general, these solutions have not been instilled more often than every two hours during the waking hours. The drops were usually well tolerated even in patients with corneal epithelial damage. On occasion the 1:3000 dilution was irritating and not accepted by the patient.

The total number of patients so treated was only 45, and it would be premature to draw any definite conclusions. Special mention should be made, however, of the use of Virac in the treatment of herpetic keratitis. A total of eight patients (one person treated twice) with herpetic keratitis have been treated with the above Virac solutions. The drug did not cure the condition. It was our impression, however, that Virac halted the development of the dendritic figures. These remained fairly stationary in appearance during treatment. This was equally true in the three persons in whom steroid therapy (topical and/or systemic) was required for severe uveitis. After observation for a few days the loose epithelium around the dendritic figures was removed mechanically (with a spatula or swab soaked with the Virac irrigant), the conjunctival sac was irrigated, and the eye was patched. Prompt healing occurred, and use of Virac drops was resumed when the patch was removed. There was no further recurrence in any patient during therapy. The one patient treated twice had been followed through several previous episodes, and it was our impression that the over-all course of the disease process was more benign when Virac was used. The course of herpetic keratitis, however, is so variable that it would be unwise to draw any definite conclusions at this time. Continued trial, however, does seem justified.

It should be noted that in two instances we transferred the virus from patients to rabbits and thence from rabbit to rabbit. The rabbits developed the typical full-blown keratitis. Treatment with Virac drops failed to arrest the process either in the active stage or when given after the inoculations but prior to the development of signs of infection.

Other virus diseases treated included one case of inclusion blenorrhea, which failed to respond. In addition, there were two cases with a clinical picture suggesting adenoidal-pharyngeal-conjunctival virus (APC) infection with corneal infiltrates that returned after cessation of therapy and promptly cleared again within 24 hours after therapy was renewed. Again, conclusions must be guarded.

The ultimate value of the product in the treatment of M. pyogenes var. aureus infections of the eye is still being assessed. A few cases of conjunctivitis due to the organism appear to have responded well. Currently, about the lids we are using a Virac ointment in concentration of 1:3000 of the quaternary base in petrolatum. It is safest to state that for this purpose the product appears to be useful.

Summary

The clinical potential of an iodophore, Virac, a mixture of elemental iodine and a cationic detergent, with potent germicidal properties has been investigated.

In the laboratory Virac proved to be less toxic than benzalkonium chloride both in vitro and in vivo.

Of all diluents tried boric acid was found to be the best from the standpoint of com-

† This is somewhat higher than the value calculated from the formula provided by the manufacturer.

patibility and stability of the iodine. Even with this diluent loss of elemental iodine occurs over a period of weeks under ideal conditions and more rapidly when the preparation is in contact with some contaminant such as metal or organic matter.

In dilutions with considerable germicidal potency Virac was not toxic to the human eye even when applied to an eye with disturbed corneal epithelium.

Virac appears to be an efficient surgical preparation. Its use around the eye prior to surgery caused no untoward local or other reactions.

Virac appears to be an excellent irrigant for the conjunctival sac and lacrimal passages, being of low toxicity while possessing high germicidal activity.

Virac is not a cure-all for ocular infections. It does not cure herpes simplex of the cornea but may be of value in its treatment.

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Cataracts in Galactosemia

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Galactosemia is an inborn error of carbohydrate metabolism first described by von Reuss [1] a half a century ago. Sporadic reports of the disorder are found in the literature since that time, and during the past decade, probably because of earlier recognition and diagnosis, such reports have appeared with increasing frequency.

The occurrence of cataracts is one of the common features of the disease, and it is the purpose of this paper to give a long-range follow-up of the eye findings in a relatively large group of cases.

Clinical Findings

Clinically, infants with galactosemia appear normal at birth, but signs and symptoms appear within a few days or weeks at most. Presenting symptoms are usually vomiting, lethargy, fever, and failure to gain weight. Icterus, ascites, peripheral edema, hepatomegaly, and splenomegaly are among the physical findings.[2] Cataracts and mental retardation may be recognized as early as 4 to 8 weeks of age.[2]

Laboratory Findings

A reducing substance in the urine and albuminuria are often present. The former may be readily identified as galactose by paper chromatography. It may also be differentiated from glucose by yeast fermentation or by the use of the specific enzyme, glucose oxidase, which can be obtained commercially as test tapes.

The presence of galactose in the urine does not always indicate galactose intolerance.[3] Galactose-tolerance tests may be necessary to establish the diagnosis. The galactose-tolerance test has been used in this series with no untoward effects. Others have considered this test dangerous, and the relatively simple spectrophotometric test [4,5] should be used whenever possible to demonstrate the specific enzymatic defect.

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Etiology

Galactosemia is an inborn error of galactose metabolism resulting from deficiency of a specific enzyme necessary for its utilization. Recent investigations have elucidated the pathway by which galactose is converted to glucose.[5-7] Three distinct steps have been described.

The first consists of the phosphorylation of galactose into galactose-1-phosphate in the presence of adenosinetriphosphate and galactokinase.

$$\text{Galactose} + \text{ATP} \longrightarrow \text{Galactose-1-P} + \text{ADP}$$

In the second step, galactose-1-phosphate is converted to glucose-1-phosphate in the presence of uridine diphosphoglucose and catalyzed by phosphogalactose uridyl transferase.

$$\text{Galactose-1-phosphate} + \text{UDPGlucose} \rightleftharpoons \text{UDPGalactose} + \text{Glucose-1-phosphate}$$

Galactose-1-phosphate is incorporated into the nucleotide, liberating glucose-1-phosphate and yielding diphosphogalactose. The catalyzing enzyme phosphogalactose uridyl transferase is missing in galactosemia, resulting in the accumulation of galactose-1-phosphate. This is the point of the metabolic block.

The third step is the conversion of uridine diphosphogalactose to uridine diphosphoglucose in the presence of diphosphopyridine nucleotide and a specific epimerase.

It is now known that galactosemia is a hereditary disease. Familial occurrence has been striking, but the exact mode of transmission of the gene is not known.[2] The condition has been considered a simple Mendelian recessive, with the afflicted child resulting from the mating of two heterozygotes. Proof is lacking, however. Holzel and Komrower[4,5] performed galactose-tolerance tests on the parents of known galactosemic patients. Of four families studied, only one revealed an abnormal test in both parents; in the other three, only one parent was affected.

The exact mechanism by which tissues are damaged in patients with galactosemia is not known. It has been suggested that galactose may interfere with the availability of glucose to the tissues.[4] This hypothesis does not explain all the clinical manifestations of galactosemia. It is more likely that the accumulation of galactose-1-phosphate resulting from the metabolic block has a direct toxic effect on such tissues as liver, spleen, brain, and crystalline lens.[4]

Cataracts have been produced for many years in laboratory animals fed galactose. Mitchell and Dodge[9] gave a 70% lactose diet to rats, and all developed cataracts. A 40% lactose diet will do the same.[10] Mitchell and Cook[11] noted regressive changes when galactose was withdrawn but not complete clearing of cataracts in rats.

Treatment

Once the diagnosis of galactosemia has been established, a substitute milk (lactose-free) diet leads to rapid recovery in the majority of cases. Thus, serious complications such as cataracts and mental retardation can be prevented by early diagnosis and correct treatment. However, Bray et al.[12] have reported a case with cataracts at 12 days of age.

Ophthalmological Findings

Cataracts associated with galactosemia involve the embryonal and fetal nuclei and are described as zonular or lamellar. McAuley[13] noted striate opacities. Bray[12] mentioned intumescence of the lens. The opacities in the present series have not been particularly dense. In fact, if the pupils were not fully dilated, it would be possible to overlook the lenticular changes, although the fundus might be fully visualized. Such opacities should be revealed by the biomicroscope, but it is extremely difficult to examine infants with this instrument. Ordinarily, heavy sedation or even anesthesia is required in order to hold their heads in the chin rest. In addition, the procedure is impractical if the patient is seriously ill. The older children have all had biomicroscopy.

McAuley[13] stated that the striate opacities observed in a patient at 6 weeks of age had resolved completely in one eye and almost completely in the other by 7 months. Johnson[14] had two cases whose opacities regressed completely. He concluded that cataracts would probably resolve themselves if milk were withdrawn from the diet at 3 months of age. Reiter et al.[15] substantiated this, and Turnbull[16] reported a case that nearly cleared within three weeks following the inception of a lactose-free diet.

The cases in our series do not bear out the possibility of regression of cataracts after treatment is started. Indeed, it is possible that the cataracts in Case 2 advanced, in spite of a presumably lactose-free diet. The earlier observations were all by ophthalmoscopy and were perhaps not as accurate as the later examinations by biomicroscopy. In Case 4 there was an apparent regression. This case is cited because it shows how thin opacities may be overlooked when it has been impossible or difficult to use the biomicroscope.

Case 4.—Lenticular opacities were discovered in both eyes of a boy in June, 1951, at the age of 6 weeks. In December, 1952, he was examined under cycloplegia with homatropine and phenylephrine (Neo-Synephrine). At that time, the following statement was made: "Media, clear; fundi, normal." In January, 1958, thin lamellar

cataracts were observed in the posterior cortex, easily visualized with the biomicroscope. Visual acuity was O. D. 20/80 and O. S. 20/60. Undoubtedly, the lenticular opacities were missed in 1952 because a struggling 18-month-old infant could not be adequately examined.

Ocular Treatment

The severity of the galactosemia, the age at which it is diagnosed, and the time at which a correct diet is instituted will all influence the degree of lens involvement. If the cataracts are dense enough, they must be treated by other than dietary measures. In the few cases old enough for manifest refraction, lenses have not improved the visual acuity, with one exception (Case 1), who is myopic.

One patient (Case 2) was diagnosed at 5½ months of age. Her galactose-tolerance curve is shown in Figure 1. A second test (Fig. 2) at 5 years of age reveals that she is still incapable of utilizing galactose.

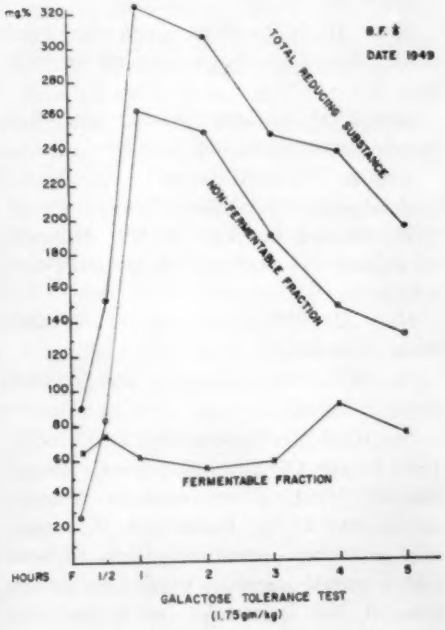

Figure 1 (Case 2)

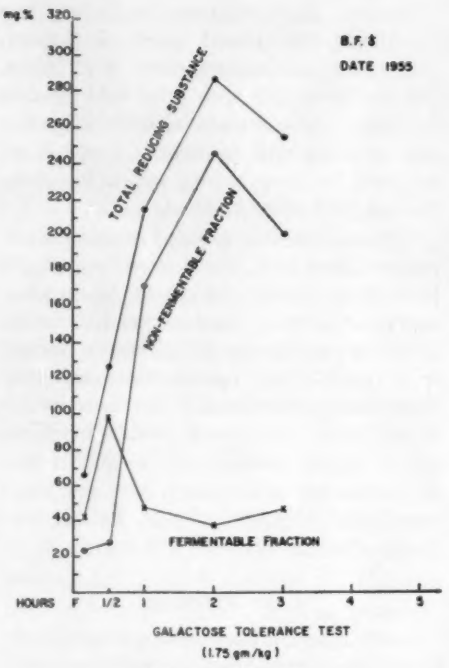

Figure 2 (Case 2)

She has had an iridectomy on each eye. Preoperative visual acuity at the age of 6½ years was 20/200 in each eye. Slit-lamp examination revealed a conoid type of posterior cortical cataract, with the apex anteriorly involving the central two-thirds of the lens. The anterior cortex was clear. The peripheral cortex showed a few fine tendrils arising from the cataract. The two lenses appeared identical.

With pupils dilated, the patient found her vision improved. For this reason, an optical iridectomy was considered justified. The right eye was operated on first, on Nov. 22, 1955. With use of general anesthesia, a keratome incision was made inside the limbus at the 12 o'clock position. A narrow complete iridectomy was performed, and the wound was closed with one black nonabsorbable surgical (silk) suture. The mother reported that the child could see much better after surgery. Therefore, a similar procedure was performed on the left eye, on Dec. 4, 1956.

On Jan. 16, 1958, the visual acuity was O. D. 20/100+1 and O. S. 20/100−1. Her vision was not improved with lenses, but she reads well with print held close to her eyes. She attends sight-saving class and is doing well in school. She has no apparent handicap at play nor in her associations with other children.

It is possible that a linear extraction will be considered later, but it seems inadvisable to handicap a child with aphakic lenses when she is so well adjusted at present. Since all of the cataracts in this series are central, it is possible that optical iridectomy may be utilized in the future if the visual acuity is sufficiently diminished. Ritter and Cannon [17] report bilateral discissions in one child, but her galactosemia was not diagnosed until 4½ years of age, and the lenticular changes were fairly dense.

Case Synopses

Cases 1 and 2 have been previously reported by Donnell [2] but are presented with subsequent ophthalmological follow-up.

Case 1.—White boy. Birth date Aug. 31, 1948. Diagnosis at 13 months of age.

Aug. 13, 1948: Admitted to Childrens Hospital, 2 weeks old. Tentative diagnosis, biliary cirrhosis (ascites, peripheral edema, and hepatomegaly).

Sept. 28, 1948: Readmitted. Diagnosis, osteomyelitis. It was noted that the right pupil was oval.

Sept. 29, 1949: Readmitted. Diagnosis, hepatosplenomegaly. Albuminuria, reducing substance in urine.

Oct. 14, 1949: Galactose-tolerance test, abnormal. Early lenticular changes, O. U., more advanced on right. Fundi, normal. Diagnosis, cataracts consistent with galactosemia. Pupil oval, O. D.

Dec. 10, 1950: Posterior cortical cataracts, O. U.

June 29, 1951: Lens opacities, no change.

Feb. 15, 1952: Opacities more marked O. D. than O. S.

March 5, 1957: O. D., pupil round with dehiscence of iris at 11 o'clock position. Fine rotary nystagmus, O. U. Examination with cyclopentolate (Cyclogyl) hydrochloride, 1%, gave the following findings: Media, entire nuclear area, O. D., was involved. Nucleus was slightly opaque, O. S. There were many punctate opacities in cortex, O. U. Fundi, essentially normal. Discs were large, consistent with myopia. Vision O. D., unimproved; O. S., $-6.50-1.25\times135=20/200$.

Dec. 14, 1957: Intelligence quotient, 93.

April 4, 1958: No change from last ocular examination.

Case 2.—White girl. Birth date, March 3, 1949. Diagnosis at 5½ months of age.

March 20, 1949: Admitted to Childrens Hospital, 2 weeks old. Diagnosis, possible sepsis, newborn, and biliary stenosis. Discharged after three weeks, undiagnosed.

Aug. 23, 1949: Outpatient clinic. Galactosemia suspected. Galactose-tolerance test, abnormal. Posterior cortical cataracts diagnosed.

1950: No change in opacities.

1951: No change in opacities.

1953: No change in opacities.

May, 1955: Lenticular opacities much denser than formerly; patient taking milk-free diet.

June, 1955: Cataracts, nuclear type, moderately dense, with clear periphery.

August, 1955: No change.

October, 1955: Visual acuity, O. D. −20/200 and O. S. −20/200. Difficulty in writing and reading, but recognition of colors.

Nov. 22, 1955: Iridectomy, O. D., Childrens Hospital.

Dec. 4, 1956: Iridectomy, O. S., Childrens Hospital.

Jan. 6, 1958: Visual acuity, O. D. −20/100+1 and O. S. −20/100−1. Fundi, normal. Slit-lamp examination: Anterior cortex clear, O. U. Posterior cortical opacities involving central two-thirds of lens, with a central convexity toward the nuclear area. A few fine tendrils or spokes came from nucleus to periphery, O. U.

Father: Media, clear; fundi, normal.

Mother: Slit-lamp examination, negative.

Sibling: Deceased. Probable galactosemia.

CASE 3.—Negro girl. Birth date, Feb. 16, 1950. Diagnosis at 5½ months of age.

July 17, 1950: Outpatient, Childrens Hospital. Complaint of "pink" urine and failure to gain weight. Admitted. Diagnosis: pyelitis, enlarged liver; galactosemia ruled out.

July 25, 1950: Galactose-tolerance test, abnormal.

Aug. 30, 1950: Few dust-like opacities, crystalline lens, O. U.

June 7, 1957: Visual acuity, 20/30 O. U. Media still show a few dust-like opacities easily seen by slit lamp.

April 4, 1958: Eye evaluation. Visual acuity, O. D. −20/25 and O. S. −20/30+. Pupils dilated with cyclopentolate and phenylephrine. Fundi, normal. Slit-lamp examination showed fine dust-like opacities in posterior cortex, O. D.; they appeared to have coalesced, forming denser opacity, O. S.

Parents: Not examined.

CASE 4.—White boy. Birth date, March 31, 1951. Diagnosis at 3 months of age.

June 19, 1951: Admitted, Childrens Hospital, 2½ months old. Diagnosis, malnutrition, neonatal icterus, suspected galactosemia.

June 23, 1951: Galactose-tolerance test, abnormal. Bilateral lens opacities consistent with galactosemic cataracts. Carbohydrate and amino acid mixture (Nutramigen) prescribed.

Dec. 26, 1952: Pupils dilated with homatropine and phenylephrine. Media appeared clear with ophthalmoscope.

Jan. 16, 1958: Retinoscopy with cyclopentolate hydrochloride, 1%, showed that vision O. D. with +0.75 sph=20/80 and vision O. S. with +0.50 sph=20/60. Fundi, normal. Slit-lamp examination, thin lamellar opacity in posterior cortex, O. U.

Father: Thirty-six years old. General health good. No history of eye problems in family. Fundi, normal. Media, few fine vitreous opacities, O. S. Visual acuity, 20/20, O. U. Slit-lamp examination, negative.

Mother: Thirty-four years old. Myopic. Fundi, normal. Media, clear. Slit-lamp examination, negative.

Sister: Case 12.

CASE 5.—White boy. Birth date, June 29, 1951. Diagnosis at 3 months of age.

Sept. 27, 1951: Admitted, Childrens Hospital, 3 months old. Diagnosis, malnutrition; projectile vomiting. Large liver, suspected galactosemia.

Oct. 1, 1951: Galactose-tolerance test, abnormal. Liver biopsy.

Oct. 5, 1951: Disciform opacities, O. U., consistent with galactosemic cataracts.

March 15, 1958: O. D. 20/50+2.00 sph, O. S. 20/50+2+2.00 sph. Fundi, normal. Media, small central opacities, O. U., seen with ophthalmoscope. Slit-lamp examination, faint haze, nuclear area, O. U.

Father: Thirty years old. Media, clear. Fundi, normal. Slit-lamp examination, negative.

Mother: Thirty years old. Had surgery, age 16, for esotropia, O. S. Vision O. D. 20/25, O. S. 20/20−3. X. T. 25△, X′. T. 20△. Media, clear. Fundi, normal. Slit-lamp examination, negative.

Brother: Eleven years old. Media, clear. Fundi, normal. Slit-lamp examination, negative.

CASE 6.—Negro boy. Birth date, Oct. 8, 1951. Diagnosis at 1½ months of age.

Oct. 26, 1951: Admitted, Childrens Hospital, 2 weeks old. Diagnosis, vomiting, dehydration, possible hydrocephalus.

Nov. 5, 1951: Discharged improved but undiagnosed.

Nov. 21, 1951: Diagnosis, cellulitis, nose and right orbit. Galactosemia suspected. Hepatomegaly, albuminuria.

Nov. 29, 1951: Galactose-tolerance test, abnormal.

Dec. 20, 1954: Opacities of lens noted, O. U.

Jan. 3, 1955: Slit-lamp examination, opacities appeared to be in posterior border of nucleus.

Jan. 16, 1958: Media appeared clear by ophthalmoscope. Fundi, normal. Pupils dilated with cyclopentolate. Slit-lamp examination, faint posterior cortical opacities. Vision O. D. 20/30 and O. S. 20/30.

Mother: Slightly myopic. Vague history of cataracts in her family.

Twin Sister: Media, clear. Fundi, normal.

Brother: Media, clear. Fundi, normal.

CASE 7.—Mexican girl. Birth date, Oct. 25, 1954. Diagnosis at 12 months of age.

Feb. 12, 1956: Admitted, Childrens Hospital, one year old. Diagnosis, malnutrition, possible miliary tuberculosis. Syphilis ruled out; possible pneumonia.

Feb. 17, 1956: Galactosemia suspected. Hepatomegaly, albuminuria, reducing substance in urine.

Feb. 23, 1956: Galactose-tolerance test, abnormal. Liver biopsy. Posterior cortical lens changes, fairly diffuse, more advanced O. D. than O. S.

Feb. 22, 1958: Crystalline lenses, no change. Fundi, fairly well visualized; essentially normal.

Father: Twenty-nine years old. Media, clear. Fundi, normal. Brother has cataracts, age 29, etiology unknown. Father has cataracts, age 59, etiology unknown.

Mother: Twenty-six years old. Media, clear. Fundi, normal.

Sister: Twenty months old. Occasional punctate opacity, O. D. Fundi, normal. Galactose-tolerance test, normal.

Four other children normal, according to parents.

CASE 8.—White boy. Birth date, Aug. 4, 1956. Diagnosis at one month of age (lactose-free diet from birth).

Aug. 7, 1956: Admitted to St. Joseph's Hospital, Santa Ana. Jaundice.

Aug. 22, 1956: Galactosemia suspected; Nutramigen prescribed.

Dec. 4, 1956: Admitted, Childrens Hospital. Galactose-tolerance test, abnormal.

Feb. 1, 1958: Media, clear. Fundi, normal.

Father: Thirty-nine years old. Media, clear. Fundi, normal. Slit-lamp examination, faint anterior and subcapsular opacities, two O. D., several O. S.

Mother: Thirty-seven years old. Media, clear. Fundi, normal. Slit-lamp examination, negative.

Sister: Sixteen years old. Media, clear. Fundi, normal. Slit-lamp examination, negative.

Sister: Three years old. Media, clear. Fundi, normal.

Brother: Not examined here. Thirteen years old. Institutionalized in midwest. Positive galactosemia, mental retardation, cataracts.

CASE 9.—White girl. Birth date, May 29, 1957. Diagnosis at 4 days of age. (lactose-free diet from birth).

May 29, 1957: Admitted, Childrens Hospital, 4 hours old. Family history of galactosemia. Rh-negative mother; Rh-positive father.

June 1, 1957: Galactose-tolerance test, abnormal.

Jan. 16, 1958: Media, clear. Fundi, normal.

Father: Twenty-seven years old. Media, clear. Fundi, normal.

Mother: Twenty-three years old. Media, clear. Fundi, normal. Myopic astigmatism.

Grandmother: Fifty-seven years old. Vision 20/30 O. U. Media, cuneiform opacities, probably senile. Fundi, early arteriosclerosis.

Brother: Five years old. Media, clear. Fundi, normal. Slit-lamp examination, faint posterior subcortical opacity, O. D.

Brothers: Two deceased. One with possible galactosemia, 1951; one with definite galactosemia, 1953.

Sister: Three years old. Normal.

Sister: Twenty months old. Normal. Has been receiving Nutramigen since birth; questionable curve on galactose-tolerance test.

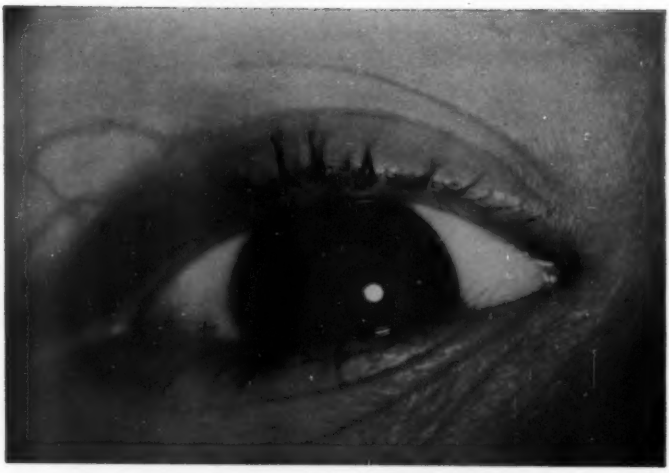

Fig. 3 (case 2).—Right eye, showing cataract and iridectomy.

CASE 10.—White girl. Birth date, Sept. 27, 1957. Diagnosis at 3 months of age.

Oct. 21, 1957: Admitted, Childrens Hospital, 3½ weeks old. Diagnosis: Sepsis; gangrene, both feet.

Nov. 5, 1957: Galactosemia suspected; Nutramigen prescribed. Eyes essentially normal; discs pale, more marked O. S.

Dec. 3, 1957: No evidence of cataracts.

Dec. 31, 1957: Galactose-tolerance test, abnormal. Definite galactosemia (not well enough to have tests until this time).

Feb. 27, 1958: Media, clear. Fundi, normal. N. B.: Gangrene had resolved except on one toe.

Father: Twenty-four years old. Media, clear. Fundi, normal.

Mother: Twenty-three years old. Media, clear. Fundi, normal.

Sister: Two years old. Media, one punctate opacity, O. S. Fundi, normal.

Grandmother: Forty-six years old. Fundi, normal. Media, fine vitreous opacity, O. S.

CASE 11.—White boy. Birth date, Sept. 20, 1957. Diagnosis at 2½ months of age.

Dec. 6, 1957: Admitted, Childrens Hospital, 2½ months old. Diagnosis, cirrhosis of liver.

Dec. 8, 1957: Galactosemia suspected. Hepatomegaly, cataracts, albuminuria, and reducing substance in urine.

Dec. 10, 1957: Galactose-tolerance test, abnormal.

Dec. 12, 1957: Media, disciform opacities, nucleus, O. U.

Feb. 27, 1958: Media, no change. Fundi, normal.

Father: Thirty-five years old. Media, clear. Fundi, normal.

Mother: Thirty-two years old. Surgery, age 6, for esotropia, O. D. Media, one punctate opacity, O. D. Fundi, normal. Refractive error, compound hyperopic astigmatism. Slit-lamp examination, one posterior subcortical punctate opacity, O. D.

Brother: Five years old. Media, clear. Fundi, normal.

CASE 12.—White girl. Birth date, September, 1952. Diagnosis at 5½ years of age. Sister of Case 4. Had lactose-free diet from birth because of brother's history of galactosemia. Media, clear. Fundi, normal. Visual acuity, not possible to determine.

March 15, 1958: Galactose-tolerance test, abnormal.

Comment

All 12 cases observed were treated by a lactose-free diet as soon as the diagnosis was established. Only one (Case 7) has not been faithful to the diet. She has eaten ice cream occasionally, but the most recent examination reveals no advance in her lenticular opacities since the time of diagnosis.

These 12 cases have been followed for periods of six months to nine years. Four have not developed cataracts, undoubtedly because of early diagnosis and immediate inception of the proper diet. These four are the following:

Case 8 was first fed with Nutramigen at one week of age by an alert pediatrician who suspected galactosemia because of jaundice, failure to gain weight, albuminuria, and a reducing substance in the urine. When the patient was 3 months of age, the diagnosis was confirmed by galactose-tolerance test.

Case 9 was admitted to the Childrens Hospital at 4 hours of age and immediately was given Nutramigen because of a strong family history of galactosemia. Diagnosis was subsequently confirmed by galactose-tolerance test.

Case 10 was admitted at 4 weeks of age because of gangrene of both feet, severe ascites, and peripheral edema. When the patient was 5½ weeks of age, the galactose-tolerance test was abnormal. She has done extremely well on a lactose-free diet.

Case 12 was first seen at 5½ years of age. Her entire family was examined at this time, and her disease was diagnosed during this routine check. Her brother

(Case 4) had been a patient at Childrens Hospital; accordingly, she received no lactose-containing food during the first year of her life. After 1 year of age she was occasionally given foods containing milk; since 2 years of age she has had one glass of milk per day, on the average.

Of the eight patients with cataracts, the earliest diagnosis was made at 6 weeks of age. In one patient diagnosis was not made until 13 months of age. None show evidence of regression of cataracts. General physical development has been excellent in all, however, the liver growing smaller and other symptoms subsiding. The older children are all attending school (two in sight-saving classes), apparently doing well.

The eyes of the parents and most of the siblings have been examined except for one case. There have been no serious ocular findings in these relatives. Fine vitreous opacities were found in two parents and occasional punctate lenticular opacities have been observed, which would be expected in any group of so-called normal persons. Two of the mothers have had eye muscle surgery, but, in general, there are no diseases of the eye which might be considered hereditary.

Conclusion

A survey of patients with galactosemia revealed two salient factors: 1. No regression of cataracts was noted in any case, even when appropriate dietary treatment was instituted immediately following diagnosis and followed faithfully, as it was by all but one patient. 2. The disease may be overlooked because of its protean clinical manifestations.

Galactosemia is primarily a pediatric problem. However, awareness on the part of the ophthalmologist may facilitate an early diagnosis.

Summary

A brief résumé of the etiology and diagnosis of galactosemia is given. Twelve cases of galactosemia are reported. Eight of these have cataracts, which are described. One patient has undergone surgery.

1930 Wilshire Blvd. (57).

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The Neurosurgeon's Role in Acute Visual Failure

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Visual failure more often than not is due to a disorder of the globe and falls within the realm of the ophthalmologist. However, a lesion that involves the optic pathways may occasionally be responsible for acute loss of vision and at times is overlooked because a thorough medical examination was not conducted when the patient first consulted his physician.[1-3] Ideally, if irreparable visual loss is to be prevented, the cause should be determined. This requires a thorough medical examination, which should include ophthalmologic investigation, the plotting of accurate visual fields, roentgenographic examination of the skull, and a complete neurologic examination. In the more difficult diagnostic problems, ancillary tests may be required if the condition of the patient can tolerate these procedures.

The records of 310 patients who came to the Mayo Clinic because of unilateral loss of vision were studied in 1953.[4] Lesions involving the retrobulbar portion of the optic nerve were noted in 108, or 34.8%, of these 310 cases. A further breakdown of the 108 cases showed that 19 (17.6%) of the patients lost their vision because of a pituitary tumor; 15 (13.9%), because of a parasellar meningioma, and 16 (14.8%), because of unverified chiasmal lesions. The combined diagnosis of craniopharyngioma, aneurysm, or other type of tumor constituted 13 (12.1%) of the 108 cases. Miscellaneous lesions of the optic pathway comprised the remaining 45 cases (41.6%) in which unilateral visual loss occurred. From these findings it is apparent that the possibility of finding a neurosurgical lesion must always be considered in the differential diagnosis of acute visual failure.

From a review of the patients who have consulted us because of this symptom, we have compiled the following list which we feel represents the commonest clinical entities that may produce sudden decreased visual acuity. Here we have attempted to list these conditions in the order of their frequency, even though they do not occur commonly.

(1) Pituitary tumor
(2) Tumor of the optic nerve or chiasm
(3) Supraclinoid aneurysm
(4) Parasellar lesion
(5) Thrombosis of the carotid artery
(6) Hydrocephalus of the third ventricle
(7) Chiasmal arachnoiditis
(8) Fracture of the anterior cranial fossa
(9) Basofrontal tumor of the skull
(10) Pseudotumor cerebri

We do not intend to review here the diagnostic features of these conditions. However, the salient clinical findings in some of them will be given in a few case reports which will be presented to illustrate diagnostic points that indicated the need for early neurosurgical intervention.

Report of Illustrative Cases

CASE 1.—A lawyer, aged 64, was apparently well until eight days before he was admitted to a Rochester hospital. At the time of admission to the hospital, he complained of bifrontal headaches which were aggravated by movement. Six days earlier the patient had had bouts of vomiting. Four days before admission he noticed loss of visual acuity in the left eye. The following day his left eyelid began to droop. Spinal

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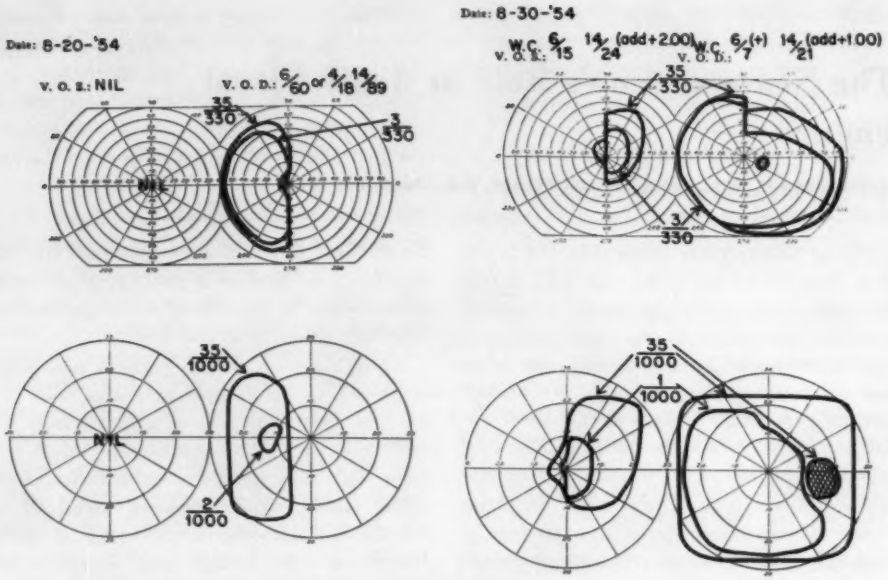

Fig. 1 (Case 1).—Plotting of visual fields. Left, at the time of initial examination. Right, nine days after operation.

puncture at home revealed increased pressure, with 80 to 90 red blood cells per cubic millimeter of spinal fluid. Generalized malaise, headache, and nausea constituted his major complaints. He was a tall man with acromegaloid facial features, but the hands and feet were normal. He was drowsy but oriented. Neurologic examination disclosed a bilateral Babinski response and complete paralysis of the left third cranial nerve, with dilatation and fixation of the pupil. Roentgenograms of the skull showed enlargement of the sella turcica, with decalcification. The basal metabolic rate was −23%. The ocular fundi were normal. The patient could only count fingers with the left eye; with the right eye he read 14/42 on the American Medical Association reading card. The visual field of the right eye was contracted temporally and below. Two days after admission there was a temporal anopsia with a central scotoma on the right and the left eye was blind (Fig. 1, left). A left carotid angiogram with cross fill with use of a 25% suspension of thorium dioxide (Thorotrast) excluded a diagnosis of aneurysm of the circle of Willis but indicated that the carotid siphon was deformed, as if by a parasellar mass. Emergency craniotomy, done on Aug. 21, 1954, on the left side, revealed bloody cerebrospinal fluid in the chiasmatic cistern. The optic nerves were bowed upward and back by a dark-colored mass. The left optic nerve was ecchymotic. After insertion of a spinal puncture needle into this mass to exclude the possibility of aneurysm, the capsule was incised and much black blood was evacuated. Intracapsular biopsy revealed chromophobe adenoma of the pituitary gland on microscopic study. All of the tumor and the capsule were surgically removed. The pathologist reported that the tumor was an infarcted hemorrhagic pituitary adenoma. Postoperatively, convalescence was uneventful. Light perception on the left was noted by the patient at the end of the second postoperative day, and the paralysis of the third nerve was lessening. Nine days after operation there was marked improvement in central vision on the left, with a filling in of most of the right temporal field and much

of the nasal field of the left eye (Fig. 1, right). Four months later the field of the right eye was almost normal and the field of the left eye was filling out. Acuity of the right eye was 6/10; that of the left, 6/12. There was no further change on examination after a lapse of another nine months.

This patient represents an example of hemorrhage into an unsuspected pituitary adenoma. His vision was saved by early diagnosis and prompt definitive surgical treatment to remove the cause.

CASE 2.—A boy, aged 12, was referred to the Mayo Clinic on Aug. 24, 1954, with a diagnosis of retrobulbar neuritis. Two weeks prior to arrival he noticed blurring vision with the left eye while target shooting. Ten days later he could not see objects with the left eye when the right eye was closed, except temporally. On arrival he complained of headache, throbbing and dull, and loss of vision in the left eye.

Medical examination gave essentially negative results. Roentgenograms of the head and optic canals showed no abnormalities. Vision of the right eye was 6/6; that of the left, perception of hand movements at 1 ft. The visual field of the right eye was full. In the field of the left eye vision was preserved only in the upper quadrants. Both optic nerve heads appeared normal. At this stage of the examinations retrobulbar neuritis appeared to be the most likely diagnosis.

On Aug. 27 the patient complained that vision of the right eye was blurred. Headaches, nausea, and vomiting began that morning. Lethargy developed. The left eye was now blind, and only a residual nasal field remained in the right eye (Fig. 2, above). The pupils were dilated; the left responded poorly to light.

Emergency craniotomy on the same day disclosed a hemangioendothelioma of the left optic nerve and left half of the chiasm with intramedullary rupture of the optic nerve. Acute hemorrhage had occurred within the hemangioendothelioma and was compressing the anterior portion of the third ventricle. The segment of involved nerve was resected from the globe to and including that portion of the chiasm on the left. Postoperative x-ray therapy was administered.

Examination on Dec. 6 showed mild pallor of the right optic disc and intense pallor of the left disc. There was considerable improvement in the field of the right eye

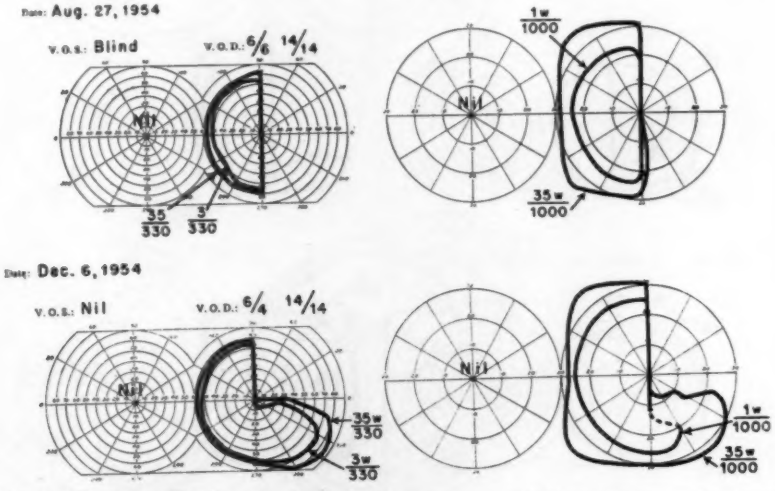

Fig. 2 (Case 2).—Plotting of visual fields. Above, on admission. Below, approximately three months after operation.

(Fig. 2, below). The fields were unchanged when last examined, on July 12, 1955.

CASE 3.—A boy, aged 10, was admitted to a Rochester hospital on Nov. 6, 1952, with a history of headaches and progressive visual loss in the right eye over a five-week period. He had been in good health until five weeks previously, when his head had been banged against the wall by playmates. Examination at home on Nov. 1 had revealed an ill youngster complaining of headache and loss of vision in the right eye. In the field of the left eye there was a loss in the upper temporal quadrant. The following day the left temporal hemianopsia was complete. The Babinski response was positive on the right. The neck was stiff, and the rectal temperature was 102 F. The peripheral leukocyte count was 12,600 per cubic millimeter of blood. Spinal puncture revealed a pressure of 114 mm. of mercury and a total protein content of 55 mg. per 100 cc. The referring surgeon reported that ventriculography performed on Nov. 3 suggested inadequate filling of the chiasmatic cistern without shift of the ventricular system.

Our ophthalmologic examination showed blindness on the right and incomplete temporal anopsia on the left (Fig. 3, above). Roentgenogram of the skull disclosed no decalcification of the sella turcica and normal optic canals. Immediate craniotomy revealed a ballooned-out right optic nerve which at first glance resembled an aneurysm. A needle was inserted, and dark blood was obtained. The nerve had been disrupted by a clot. A biopsy specimen contained a Grade 1 telangiectatic astrocytoma. The optic nerve was divided distal to the mass at the optic foramen, which was enlarged, and the right nerve and the right half of the chiasm were resected. Postoperative examination of the visual fields on Dec. 18, 1953, demonstrated improvement in the field of the left eye (Fig. 3, below) and showed a central visual acuity of 6/5 in the left eye. Examinations in 1954 disclosed no change.

The story in this case is one of a progressive chiasmal lesion beginning prechiasmally on the right and extending to involve the chiasm. Trauma to the head may have produced hemorrhagic disruption of the nerve and the rapid visual loss.

CASE 4.—A woman, aged 52 years, was sent to the Mayo Clinic on Jan. 2, 1957, with a diagnosis of multiple sclerosis. She

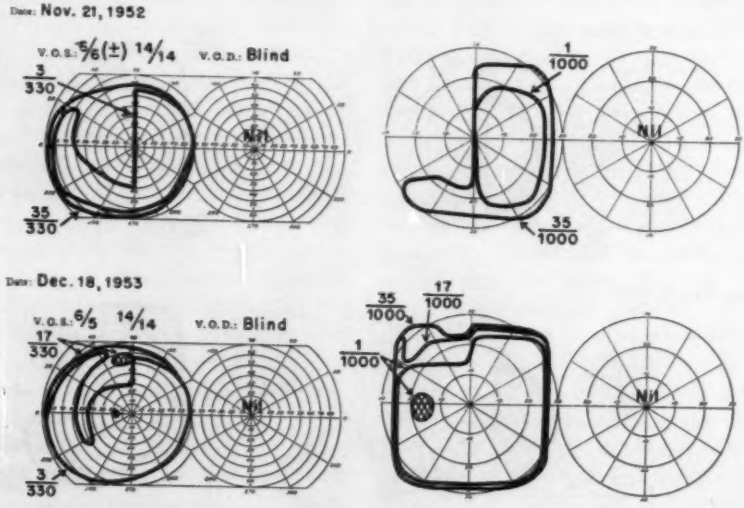

Fig. 3 (Case 3).—Plotting of visual fields. Above, on Nov. 21, 1952. Below, on Dec. 18, 1953.

had noticed blurring of vision in the temporal field of the right eye in the summer of 1953. This had not progressed. In May, 1956, she had begun to notice blurring of vision in the left eye, and this had been progressive to the present time. She had been unable to read newsprint since November, 1956. Two pneumoencephalograms at home were reported as disclosing no abnormality. The spinal fluid contained 107 mg. of total protein per 100 cc.

General medical examination revealed only obesity and hypertension. The systolic blood pressure was 180 mm. of mercury, and the diastolic, 130 mm. The patient denied having headaches, polyuria, loss of pubic or axillary hair, or other signs of pituitary dysfunction. Neurologic examination gave completely negative results except with reference to the visual pathways. Ophthalmoscopic examination disclosed moderate pallor of the right disc and mild pallor of the left disc; the retinal arterioles were extensively narrowed, with minimal sclerosis and focal constrictions. Examination of the visual fields (Fig. 4) revealed bitemporal hemianopsia, indicative of a chiasmal lesion. The ophthalmologist did not believe that this was attributable to multiple sclerosis.

On Jan. 7, 1957, bilateral carotid angiography was carried out. This showed a large aneurysm of the right internal carotid artery beneath the right anterior clinoid process (Fig. 5). There was cross filling from left to right. The aneurysm appeared bilobate.

On Jan. 12, through a right transfrontal craniotomy, an infraclinoid carotid aneurysm was exposed and trapped intracranially. The

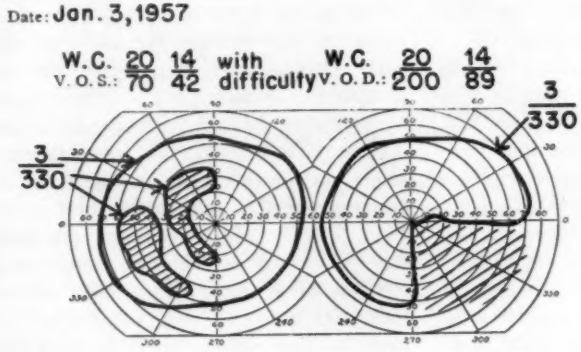

Fig. 4 (Case 4).—Visual fields plotted on Jan. 3, 1957.

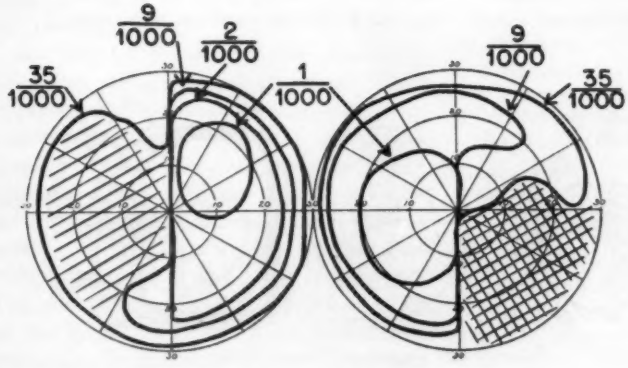

Fig. 5 (Case 4).—Carotid angiogram with 50% diatrizoate (Hypaque) solution, demonstrating bilobed aneurysm of the right carotid artery.

aneurysm elevated the optic chiasm and the right optic nerve, which had grooved the aneurysm into its bilobate form.

Ophthalmodynamometric studies on Jan. 16 revealed a pressure of 35 mm. of mercury in the right retinal artery and 52 mm. in the left. Two weeks after operation there did not seem to be any noticeable improvement in visual acuity or the visual fields, even though the size of the aneurysm and its tenseness were reduced by the surgical procedure.

Case 5.—A man, aged 43, was admitted to the Mayo Clinic on Feb. 13, 1958, complaining of blindness in the left eye and recent visual loss in the right eye. He had first noticed blurring of vision in October, 1957. Vision apparently improved somewhat, and the tentative diagnosis was retrobulbar neuritis. In December, 1957, he received corticotropin (ACTH) intravenously, and he believed that this definitely improved his vision. Late in December he began to notice a little diminution of vision on the right. In January, 1958, a pneumoencephalographic examination was done at home; however, there was not enough air in the chiasmatic cistern to permit an accurate diagnosis. The interventricular septum was not displaced.

Ophthalmologic examination on Feb. 14, 1958, disclosed that the left eye was blind. The eye movements were normal. The ocular fundi were normal, and the discs were of good color. Plotting of the visual field of the right eye showed anopsia (Fig. 6). X-ray examination of the skull and of the optic canals gave negative results.

The history of several rapid losses of part of the vision, followed each time by a slow recovery, was strongly suggestive of chiasmal retrobulbar neuritis, but the slow progression of visual loss indicated a possible parasellar mass. A left carotid angiogram on Feb. 19 demonstrated a suprasellar mass, larger on the left than on the right, with elevation of the anterior cerebral arteries (Fig. 7). A left transfrontal craniotomy was performed on Feb. 21, with subtotal removal of a craniopharyngioma, adamantinoma type, on the left side of the sella turcica. The patient made a satisfactory postoperative recovery. Examination of the visual fields on Feb. 28 (Fig. 8) showed the field of the right eye to be normal and the field of the left eye to contain a

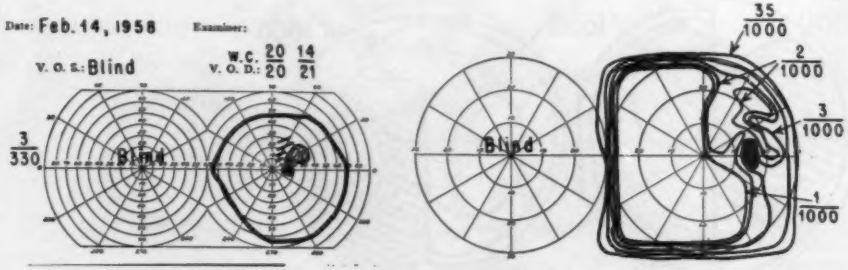

Fig. 6 (Case 5).—Visual fields plotted on Feb. 14, 1958.

Fig. 7 (Case 5).—Carotid angiogram with 50% diatrizoate solution, demonstrating elevation of both anterior cerebral arteries.

ritis or multiple sclerosis is not uncommon in a hasty evaluation of the complaint of a patient whose visual acuity is decreasing rapidly. This mistake may result in irreparable damage to the optic nerve before the correct diagnosis is made, so that definitive surgical treatment produces a discouraging result.[5]

Several case reports illustrate the difficulties of diagnosis that confront physicians in the management of these problems. The pitfalls of hasty diagnosis are obvious, and, unfortunately, in many instances definitive treatment cannot be expected to do more than prevent further visual loss, since the type of lesion of necessity prevents restoration of vision. Occasionally an apparently hopeless situation can be rectified, and this justifies the judicious search for lesions

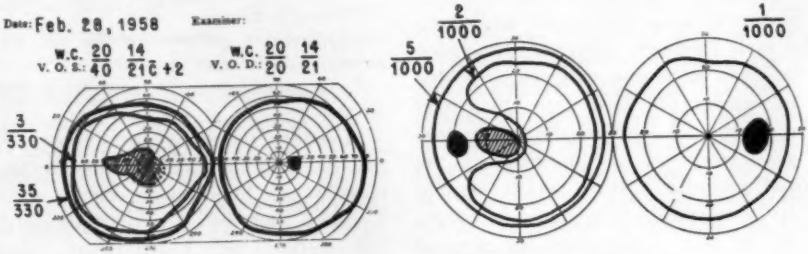

Fig. 8 (Case 5).—Visual fields plotted on Feb. 28, 1958.

temporal scotoma. At the time the patient was dismissed, on March 3, the vision was 20/20 in the right eye and 20/40 in the left. Both optic discs remained of good color.

Summary and Conclusions

An analysis of some of the clinical entities that will produce acute visual failure is presented to illustrate the need for prompt neurosurgical intervention if irreparable damage to the visual system is to be prevented. The need for a complete and accurate medical, neurologic, and ophthalmologic investigation in any of these conditions is apparent, and every effort should be made to make the correct diagnosis early, so that definitive treatment can be instituted promptly. A diagnosis of retrobulbar neuritis that can be treated successfully by surgical intervention.

Mayo Clinic.

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The Effect of Tonography and Other Pressures on the Intraocular Blood Volume

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Tonography has become a recognized test in clinical ophthalmology and the source of much experimental and scientific information. It is simply a method of pushing fluid out of the eye by a given weight in a given time. The problem discussed in this paper is What fluid?—Is it entirely aqueous or partly aqueous and partly blood?

The fact that the application of a tonometer to an eye for a period of time caused the pressure to drop was known to Schiøtz and his early followers. Wegner [1] concluded that the drop in tension was primarily due to displacement of blood from the uveal system. Bailliart [2] felt that the fall in tension was from the modification of the choroidal vascular system, which allowed itself to be flattened. Subsequent investigators have supplied ample proof that external pressure in the form of tonometry displaces aqueous from the eye, but the role of possible changes in the volume of blood inside the eye with the application of the tonometer has never been precisely defined.

When a tonometer is placed on the eyeball, a succession of changes take place. There is flattening of the peripheral cornea by means of the footplate and indentation of the central cornea by the plunger. This displaces fluid for which some new space is found by distension of the sclera, but the relative resistance of the wall results in an increase in tension. The scleral resistance forces fluid out of the eye.[3] Tonography denotes ocular fluid loss from artificially produced rises in tension. Grant,[4] using data from Friedenwald, expressed these changes in the following well-known formula:

$$C_o = \frac{\Delta V}{T(P_{t_{av}} - P_o)}$$

where

C_o=facility of aqueous outflow

ΔV=change in volume of the eye

T=time in minutes

$P_{t_{av}}$=average pressure in the eye with the tonometer on the eye

P_o=pressure before the tonometer is placed on the eye.

However, the above formula is a simplified one and makes the following assumptions [5]: (*a*) There is no change in rate of secretion and diffusion of aqueous during tonography. (*b*) There is no change in volume of blood in the eye during tonography. (*c*) Episcleral venous pressure during tonography is the same as in the undisturbed eye. (*d*) The facility of aqueous outflow with a tonometer on the eye is the same as that in the undisturbed eye. The more precise formula would be written as follows:

$$C_o = \frac{\Delta V_s + \Delta V_c + \Delta V_b + FT}{T(P_{t_{av}} - P_o - \Delta P_v)}$$

where

ΔV_s=change in scleral distension during tonography

ΔV_c=change in corneal indentation during tonography

ΔV_b=change in blood volume during tonography

ΔP_v=change in episcleral venous pressure

F=rate of aqueous inflow and outflow.

The changes in scleral distention (ΔV_s) and corneal indentation (ΔV_c) have been investigated by others. It is the purpose of this study to investigate possible changes in

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the volume of blood during tonography—ΔV_b in the above equation.

ΔV_b has been assumed to equal zero and has been ignored because of Grant's findings that the coefficient of aqueous outflow was of the same magnitude for normal eyes as for eyes that are dead and enucleated.[4] This was felt to demonstrate the minimal influence of blood volume changes.[6]

This assumption has been questioned because of certain phenomena observed in living eyes:

1. Marked external pressures as produced by the ophthalmodynamometer of Baillairt result in obvious changes in intraocular blood volume that can be observed with the ophthalmoscope.[2,7,8]

2. Increasing the intraocular blood volume as Wessely [9] did by placing a ligature around the neck or as Adler [10] did with a ligature around the aorta resulted in an increase in intraocular tension.

3. Decreasing the intraocular blood volume as Bárány [11] did by unilateral closure of the common carotid artery reduced the intraocular tension.

4. Some drugs that seemed to alter intraocular blood volume also produced changes in tension.[12,13]

Although none of the foregoing are at all conclusive, each suggests that the intraocular blood volume may change during tonography and that the assumption that $\Delta_b=0$ is not justified. Further insecurity results from the fact that the blood volume of the living eye is not known. Ridley [14] attempted to measure the blood volume by an interesting method. He connected a manometer set at 22.5 mm. Hg pressure to an animal's eye with an open stopcock and a measuring pipette with a visible bubble between the eye and the reservoir. He then opened the animal's heart. The intraocular pressure was maintained as a constant, and therefore as the blood left the eye the fluid flowing in through the measuring pipette indicated the amount of blood lost. We attempted to duplicate this experiment but could not arrive at a steady state after the blood was drained and therefore felt that the results were unreliable. Becker and Friedenwald estimated the blood volume of the human eye to be 200 cu. mm. from a study of histological sections.[5]

We adopted a method for the measurement of changes in intraocular blood volume in the living eye by the use of radioactive phosphorus (P^{32}) and have used it in studies of drugs and other factors that might influence the blood volume within the eye.[15] The technique may be briefly summarized as follows [16]: Blood, 10 cc., is withdrawn from the experimental animal, mixed with 2.0 mc. of P^{32}, and incubated at 37 C for two hours, during which time it is gently agitated. The blood is centrifuged; the red cells are removed and washed three times with saline to remove any P^{32} that is outside the cell. The red blood cells are then resuspended in saline and reinjected into the experimental animal. As all of the P^{32} is now contained within the red blood cells and all of the red blood cells are contained within blood vessels, the radioactivity comes only from the blood stream and will vary directly with the volume of blood contained within the vessels in the area. A Geiger-Müller probe is placed on the eye to detect the radioactivity.

If sufficient pressure to force blood out of the eye is applied, the counting rate of radioactivity will fall. This pressure may be applied externally by a tonometer or orbitonometer or internally through a needle in the anterior chamber connected through a manometer with a reservoir of fluid. This enabled us to correlate the effects of external pressure with known changes in intraocular tension and study the effects of each on the intraocular blood volume. As the aqueous and vitreous were not radioactive, any changes in fluid volume other than blood would not be recorded.

Cats were used throughout this study for several reasons: 1. Cats had been used in most of our previous work, and we felt more familiarity with the experimental technique in these animals. 2. Friedenwald's

TABLE 1.—*Summary of Changes in Blood Volume from Tonometry and Orbitonometry* *

	Tonometer				Orbitonometer		
	5.5 Gm. (11 Eyes)	7.5 Gm. (14 Eyes)	10 Gm. (16 Eyes)	15 Gm. (14 Eyes)	50 Gm. (18 Eyes)	100 Gm. (12 Eyes)	200 Gm. (14 Eyes)
1	10	23	10	10	25	54	22
2	0	19	14	19	44	47	59
3	0	37	25	35	47	18	93
4	0	0	9	10	14	66	118
5	0	0	23	18	76	43	106
6	0	0	25	0	32	27	80
7	0	0	25	0	45	66	126
8	0	0	0	0	104	44	100
9	0	0	0	0	114	157	30
10	0	0	0	0	52	66	80
11	0	0	0	0	19	137	100
12		0	0	0	68	63	80
13		0	0	0	41	None without change	243
14		0	0	0	33		161
15			0		29		None without change
16			0		120		
17					71		

* Recorded in per cent change compared with count before weight.

calculations for the 1954 scale for the standardization of tonometers were largely performed on cats.[17] 3. The average thickness of the cat cornea and the type of intraocular circulation are more nearly like those of the human than are those of other experimental animals.

The effects of external pressure on the intraocular blood volume were studied first.

Routine tonographies were performed with a standard Schiøtz tonometer, with use of weights of 5.5, 7.5, 10.0, and 15.0 gm. on cat eyes. The animals had previously been prepared according to the technique described above for P^{32}. A number of experiments were discarded at the outset because of technical errors, such as misplacement of the Geiger-Müller tube. After technical difficulties were solved, 55 animals were tested in this manner. The results of these experiments are summarized in the first four columns of Table 1.

External pressure greater than that applied during tonography was made with the orbitonometer. Pressures of 50, 100, and 200 gm. were applied to the prepared cat eyes. Forty-four animals were used in this phase of the experiment. Results are tabulated in the last three columns of Table 1.

These experiments show that the pressure exerted by a tonometer with a 5.5 gm. weight (total weight 16.5 gm.) is not sufficient to alter the intraocular blood volume in 10 of 11 animals, that is, $\Delta V_b = 0$. The actual change in intraocular tension produced by a tonometer with a 5.5 gm. weight may be estimated from the tables of Friedenwald given by Moses and Becker [18] showing the values for P_t and P_o. At a scale reading of 3, these are 37 and 24 mm., respectively, and thus a change of intraocular pressure of approximately 13 mm. Hg results from the application of the tonometer with this weight. The change in tension in millimeters of mercury within the eye for various weights at scale readings of 3 are shown in Table 2.

When tonography was performed with a 7.5 gm. weight, 11 of 14 eyes showed no change, although the other 3 showed an average change of 26.5% of the original count (Table 1, Column 2).

When tonography was performed with a 10 gm. weight, 9 of 16 eyes showed no change and the remaining 7 showed an average change of 19.4% (Table 1, Column 3).

TABLE 2.—*Changes in Intraocular Tension with Various Weights on Schiøtz Tonometer (Scale Reading 3)*

Weight, Gm.	P_o	P_t	Changes in Intraocular Tension
5.5	24	37	13
7.5	36	50	14
10	51	67	16
15	81	101	20

Tonography with a 15 gm. weight resulted in no significant change in 9 of 14 eyes, and the remaining 5 averaged 18.4% change (Table 1, Column 4).

When greater external pressures were applied with the orbitonometer, the changes in intraocular blood volume were much more consistent and much more marked.

Fifty grams of pressure under such conditions resulted in changes in 17 of 18 animals, and the average percentile change was 53.47% (Table 1, Column 5). One hundred grams produced changes in all 12 animals tested, and the average was 65.2% change. Two hundred grams likewise changed the blood volume in every animal tested, 14 of 14, for an average percentile change of 99%.

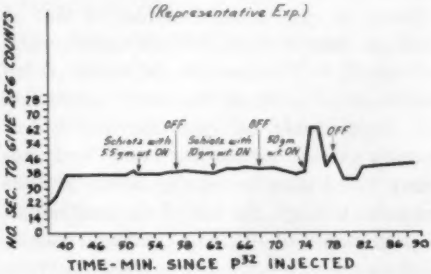

Fig. 1.—Representative experiment showing effect of pressure by tonometer and orbitonometer.

Two representative experiments have been charted in Figures 1 and 2. The counting rate is plotted against the time, and the effects of applications of the Schiøtz tonometer with 5.5, 10, and 15 gm. weights and the of orbitonometer with pressures of 50 and 100 gm. are illustrated.

The foregoing demonstrates that tonography with a 5.5 gm. weight results in no significant change in blood volume. Tonography with heavier weights resulted in changes in a minority of animals. These may have had more labile vascular systems or may have been more susceptible to pressures. But, even with tonography with weights of 15 gm., the majority showed no change. An over-all average for tonography with any weight was less than 10% change.

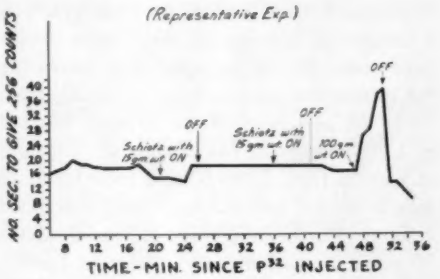

Fig. 2.—Representative experiment showing effect of pressure by tonometer and orbitonometer.

When greater pressures were applied through orbitonometry, very significant changes in intraocular blood volume did occur. In all but one eye in the groups subjected to 50, 100, and 200 gm. of pressure there were changes, and these changes were very significant.

We felt that it would be interesting to measure changes in blood volume resulting from alterations of intraocular tension produced by a fluid reservoir connected through a manometer to a cannula in the anterior chamber. In all cases, the anterior chamber was cannulated with the stopcock open and the fluid level adjusted to deliver approximately 22 mm. Hg pressure. A base line of radioactivity was obtained with the pressure at this level. The fluid reservoir was then gradually raised so that the intraocular tension was increased in increments of 10 mm. Hg. The results can be best

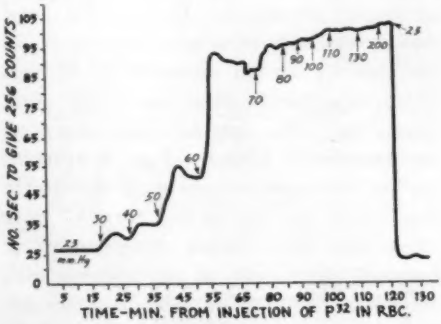

Fig. 3.—Decrease in blood volume caused by increasing the intraocular tension (shown in millimeters of mercury) by raising the fluid reservoir attached to a cannula in the anterior chamber.

appreciated from Figure 3. This graph is a composite drawing of the results of experiments. It will be noted that increasing the intraocular tension from 23 to 30, from 30 to 40, and from 40 to 50 mm. resulted in little change in blood volume. Changes in tension from 50 to 60 and from 60 to 70 mm. produced very marked changes in blood volume. Further increases in tension above 70 mm. resulted in only moderate further reductions in blood volume. When the intraocular tension was returned to the original level, the blood volume returned to the original base line or lower.

The tonography, orbitonometry, and manometer experiments all indicate that there is a certain critical level that displaces a considerable amount of blood from the eye. This level in cats' eyes is in the neighborhood of 50 mm. Hg pressure *in the eye*. Changes in intraocular tension below this level result in relatively slight alterations in intraocular blood volume. Further increases much above this tension range result in only moderate additional decreases in intraocular blood volume.

We wish to point out again that placing a Schiøtz tonometer with a 5.5 gm. weight (total weight 16.5 gm.) on an eye increases the intraocular tension by 13 mm. Hg. If the intraocular tension before application is 23 mm., it is thus raised to 36 mm. by the application of the tonometer. The same instrument with a 15 gm. weight increases intraocular tension by 33 mm. Hg., and thus an eye with an original tension of 23 mm. has its tension increased to 56 mm. These experiments show remarkably good correlation. The external applications of tonometers with 5.5 and 7.5 gm. weights all resulted in tension changes in the manometer group from 23 mm. to less than 41 mm., where little blood volume change occurred. External application of tonometers with weights of 10 and 15 gm. results in increase in intraocular tension in the range of 50 mm., where the changes in blood volume were noted to begin with the manometer. No tonometer applications increased the intraocular tension to 60 mm., where the marked changes in blood volume occurred. Orbitonometer applications did fall within this group, and marked alterations in blood volume occurred.

Having determined the pressures that do and do not significantly alter blood volume in the cat eye, it seems necessary to answer two other questions: 1. Can these findings on a cat be transferred to humans with some reliability? 2. Is the volume of blood in an eye sufficient that altering it would significantly influence the general fluid dynamics?

We believe that these findings based on experiments in the cat eye do indicate the pressure relationships in humans for the following reasons: 1. The intraocular circulation in cats is more similar to that of humans than is that of most experimental animals.[19] 2. Friedenwald did much of his experimental work on tonometry calibration (P_t coefficients) on cats and found reasonably close values for cats and humans.[20-22] 3. Studies of the retinal arterial pressure through the use of the ophthalmodynamometer of Bailliart indicate reasonable correspondence between the cat and the human, although the magnitude of error with this instrument is great.[23,24] It has also been demonstrated that the retinal arterial pressures are related to the systemic arterial pressure. The diastolic retinal pressure is approximately 45% and the systolic, approximately 55% of the brachial pressure. Human blood pressure is approximately the same as that of cats. We found the cat systolic pressure to be 100 to 130 mm. Hg, by placing a cannula in the femoral artery.

The volume of blood in the living eye is not easy to determine. We approached the problem in the following manner.

The counting rate of radioactivity in a given animal over the choroid and retina posterior to the ora serrata was established. The area under the Geiger-Müller probe was calculated. Blood from the same animal was placed in a tiny well and covered with sclera,

and counts were made with the same probe. Blood was added to the well until the counting rate was the same as that obtained in the living eye. The blood in the well was weighed. The areas of choroid and retina were calculated geometrically from measurements of the diameters of the cat eye and the distance from the line dividing the ciliary body and choroid to the posterior pole. The amount of blood in the living eye posterior to the line dividing the ciliary body and the choroid was 89 cu. mm. (average of four animals). No attempt was made to calculate the blood in the iris and ciliary body. It is interesting to compare this figure with that of 200 cu. mm., which Becker and Friedenwald [5] estimated from histological studies as the volume of blood in the human eye, and that of 210 to 250 cu. mm., estimated by Ridley.[14]

We also attempted to determine the total blood volume of the cat eye by giving the animal radioactive chromium (Cr^{51}), which is readily confined to the blood stream. A sample of blood was taken from the animal, and the radioactivity per second per gram was calculated. The eye was enucleated with a tonsil snare to minimize blood loss and immediately dropped into a freezing mixture. Extraocular tissue was dissected from the globe, and the entire globe was placed in a well-type counter. Calculations from four eyes gave the following figures for cubic millimeters of blood volume: 33, 45, 32, and 27 cu. mm., an average of 34 cu. mm.

In light of the fact some blood is lost from the eye by the Cr^{51} method and that neither method can be expected to have a greater accuracy than a factor of 50%, we feel that the figures of 89 cu. mm. for the posterior area of the living eye and 34 cu. mm. for the enucleated eye show reasonable correspondence. Both of these values indicate that the volume of blood in the eye is very much less than the volume of aqueous. We found that the volume of aqueous in the cat eye averaged 770 cu. mm. This would tend to minimize the significance of ΔV_b.

Summary

Studies with P^{32} and Cr^{51} allow us to conclude that the volume of blood in an eye is very much less than the volume of aqueous. External pressure of the amount exerted by the Schiøtz tonometer with weights of 5.5 and 7.5 gm. change the blood volume little, if at all. The same instrument with 10 and 15 gm. weights may alter the blood volume slightly but probably not significantly. Greater pressures, as applied with the orbitonometer, do alter the intraocular blood volume to marked degrees. These findings correlate well with those obtained by changing the intraocular tension with a cannula in the anterior chamber.

Although the experimental work was performed on cats, it is reasonable to conclude that the findings may be transferred to humans.

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A Scleral Imbrication Technique

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It is our purpose in this paper to describe a technique of scleral shortening with incarceration of a hinged roll of sclera. This procedure was evolved to obtain the advantages of a reduced scleral arc and a large and long-lasting choroidal fold without introducing a foreign body such as a plastic tube.

From 1954 to 1958 we have operated on 97 cases, using the following method.

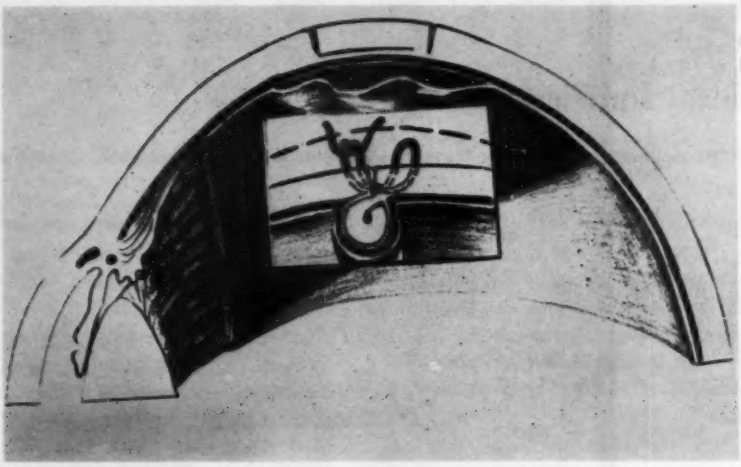
To obtain adequate scleral exposure a conjunctival incision is made 10 to 12 mm. from the limbus. If the area to be operated on is confined to one quadrant, an episcleral traction suture is used; if there is more than one quadrant requiring surgery or if the optimum area for operation straddles a muscle, this rectus muscle is detached and a traction suture is placed through its tendon stump on the sclera.

The location and extent of the scleral incisions will of course be determined by the position of the retinal breaks. The main choroidal fold is placed so that the retinal break will lie on the anterior slope of the fold. The commonest practice has been to place the anterior edge of the scleral defect we propose to make 13 mm. from the limbus as measured on the arc. The posterior boundary is 3 to 5 mm. behind and parallel to the anterior boundary. These two borders are outlined with a Gill corneal knife. The two lines are brought together in a point at the ends by curving the posterior line forward to meet the anterior one, making a crescent. The individual crescent is never more than 150 degrees in length. However, we have upon occasion used both superior and inferior crescents, making almost a 360 degree fold.

After the outlined area is inspected and deemed satisfactory in extent and location, the anterior incision is deepened to the point that a definite grayish-blue layer is seen. In this area a plane of cleavage to undermine the scleral flap is readily found. This undermining requires very little sharp dissection; it is carved out by a freeing and pushing-back motion. The undermining is carried posteriorly to and a little behind the second line. This posterior incision has not been deepened beyond its original shallow outline, and so the sclera between the two does not become a loose piece to be removed but remains hinged posteriorly.

At this point interrupted mattress sutures are placed across the scleral crescent. For these we use a double-armed 0000 nonabsorbable surgical (silk) suture with Davis and Geck CE-2 cutting needles. The short radius of curvature of this needle is helpful in getting the needle started in the proper location. The suture is started 1 to 1.5 mm. behind the shallow posterior groove and is brought out in this groove. The anterior bite starts through the scleral edge and emerges 1 to 1.5 mm. from this lip. These sutures are placed the entire length of the crescent and are 1.5 mm. apart, with an equal distance separating the individual suture arms.

The sclera within this crescent is pushed against the posterior lip, and surface diathermy is applied to the thinned sclera and underlying choroid. This application is kept very light and of surface type only. A seal line of a staggered double row of partially penetrating diathermy points is placed around each end of the ellipse and carried forward to the region of the ora serrata. Several penetrating punctures are made anterior to the crescent, and occasion-



ally one or two, in the groove itself. These provide the drainage.

The mattress sutures are now tied. Care must be used here to be sure the roll of hinged sclera is buried beneath the newly approximated scleral edges. This gives the effect shown in cross section in the Figure. Closure of the scleral defect is not always easy. It can be facilitated by holding all the sutures in one hand and firmly massaging the anterior to the posterior scleral lip with a muscle hook. Additional help can be given by an assistant, who directly approximates the edges with one or two forceps. If these methods fail or if intraocular pressure suddenly rises, as noted by corneal edema or resistance to dimpling with an instrument, paracentesis is done.

Even though we believe that one small group of retina cases can not accurately be compared with another group and that statistics in such a heterogeneous group as ours are particularly apt to be misleading, the question logically arises as to what the results with the described procedure were.

Our indications for this operation have been as follows: aphakic detachment, large disinsertion, vitreous bands and contractures, marked retinal shrinkage and star folds, and previous unsuccessful retinal surgery. Of our cases, 64 have been followed for at least six months well enough to report on. Of these, when last seen, 26, or 40%, had the retina in place. Short-term follow-ups also are very misleading, because of 24 cases followed a minimum of two years only 7, or 29%, had the retina still attached.

In comparing the postoperative fundus appearance of this group of patients and an earlier smaller group operated on by the usual lamellar resection technique, we believe that the choroidal fold in this group is more prominent and of longer duration. The fold gradually flattens over a period of from 12 to 24 months to a wave rather than an abrupt elevation. While we will not attempt to make statistical comparison of results with the earlier group, because of the small series, it is our impression that the results with the scleral fold are better.

One complication worthy of mention is that placing the fold too far posteriorly on the temporal side has resulted in vertical retinal folds involving and distorting the macular area. Other than this, we have encountered no complications of this procedure that one could say were in any way peculiar to the procedure.

In summary, a technique of scleral resection and incarceration of a roll of sclera is described that we feel has given better results than resection alone.

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An Evaluation of Postoperative Ophthalmoscopy After Retinal Detachment Surgery

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Introduction

Although a great deal has been written and spoken about the importance of ophthalmoscopy in the diagnosis of retinal detachments, practically all of this discussion relates to the preoperative examination. The importance of adequate postoperative examination can be emphasized when it is realized that 30% to 40% of primary retinal detachment operations are failures. It is possible to achieve cures in 50% of these initial failures if reoperations are properly planned and executed, bringing the final percentage of cures to 80% to 85%.

Postoperative ophthalmoscopy is more difficult than preoperative examination for several reasons: 1. In the early stages, the visibility of the fundus is poor because of the increased haze of the media, mainly in the cornea and vitreous. 2. Important new factors, which require interpretation, have been introduced, namely, the diathermized fundus areas and the possible presence of the roll of a scleral resection.

It is generally agreed that the earlier failure is diagnosed and the findings are properly evaluated the sooner a secondary operation can be planned and the greater its chance of success. While a reoperation at any time is not simple, clinical experience indicates that reoperation in the first week or two is easier than operations one or two months postoperatively. One reason for this is that after 14 to 21 days the sclera becomes soft in the areas of the diathermy, which increases the hazard of rupturing it during surgery. A second reason is that after the first few weeks there is an increased degree of adhesiveness and vascularity of Tenon's capsule and episclera, making it difficult to dissect down to the sclera and causing considerable bleeding to obscure the operative field during the dissection. These changes persist for several months.

Methods of Examination

It is common practice to defer the first examination of the fundus until the sixth or seventh day after surgery. A reason for this delay is the fear that eye movements may interfere with reattachment of the retina. It is my opinion, based on observations of patients operated upon at our hospital as well as at others, that early examination does not jeopardize the result. This is especially true if a scleral buckle has been created. Fundus examination in the latter group of cases shows the retina to be immobile with ordinary eye movement.

It is probably wise to minimize the eye movements during the examination. This is best accomplished by having the patient hold his index finger at some distance in front of his face prior to opening his eyes. He is then told to open his eyes and fix on the finger. If different positions of the eye are required, the examiner moves the target finger to the desired position. This minimizes the marked vitreous-retinal tug inherent in the high speed acceleration and deceleration of random eye movements.

A second reason for delay in postoperative ophthalmoscopy is poor visualization of the retina due to haziness of the media. This may be a considerable obstacle when direct ophthalmoscopy is used.

The ordinary 3 volt battery-illuminated direct ophthalmoscope provides such poor illumination that even a mild haziness of the media prevents proper visualization of the retina.

The 6 volt American Optical Company Giantscope gives better illumination, but, under difficult circumstances, it is still inadequate.

The 12 volt Keeler Pantoscope gives the brightest illumination of the direct ophthalmoscopes and, in certain cases, is of value. However, even with this instrument it is difficult or impossible to evaluate the fundus if the media are moderately hazy. The small visual aperture provided to the examiner is a disadvantage, and the large diameter of the handle and head offer an additional obstacle to getting close to the patient for examination of the periphery of the fundus.

The brighter light, larger field, and minimal distortion of the Schepens binocular indirect ophthalmoscope make it possible to study the fundus even on the first or second postoperative day. Stereopsis and great depth of focus are further advantages of the Schepens ophthalmoscope. Efficient use of binocular indirect ophthalmoscopy permits better evaluation than with any other instrument.

Ophthalmoscopy is best done in a darkened room. If evaluation is difficult and the room cannot be made sufficiently dark, it may be worth while to plan the examination in the evening, when sufficient darkness can be obtained.

It is helpful to have a widely dilated pupil, regardless of the method of examination used. Atropine, 1% or 2%, should be instilled daily. If persistent middilatation of the pupil remains for several days 10% phenylephrine (Neo-Synephrine) should be instilled two or three times a day to obtain better dilatation and also to help prevent the development of posterior synechiae. Ointments should be avoided, because they create a hazy corneal film and interfere with ophthalmoscopy, at times for one or two days after instillation.

Value of Drawings

Frequent postoperative sketches of the fundus are of great value in following a patient by ophthalmoscopy. The sketch, which should not take more than a minute, need not be detailed. It should show the extent of remaining elevated retinal areas in relation to a fixed landmark, e. g., an area of diathermy, blood vessels, a hemorrhage, or a scleral resection. Being able to compare these sketches from day to day is considerably more reliable than the vagaries of one's memory as one tries to recall the exact extent of a residual detachment a few days previously.

Postoperative Findings in Successful and Unsuccessful Cases

The position and appearance of the retina immediately after completion of surgery should be observed before the patient leaves the operating room. It should be noted whether the retina is completely flat, whether there are fluid pockets which elevate the retina, and the relationship of such pockets to the retinal breaks, scleral buckle, or other fixed landmarks. It is most important that the retina should be close to the diathermized area of choroid at the conclusion of the operation.

In the ideal case practically all of the subretinal fluid is evacuated at the time of surgery. Ophthalmoscopy on the operating table shows the retina to be entirely flat or almost so. Examination on the second postoperative day should show the retina to be completely flat and the breaks adequately encompassed by diathermy. If this picture is not found, the retina might still become reattached, but the possibility of failure has to be considered.

It should be noted that the amount of postoperative reaction externally in the conjunctiva and lids is no clue to the success or failure of an operation.

It is not always easy to decide whether the retina is detached postoperatively. The most important clue in deciding whether the retina is attached or detached is to differentiate the choroidal from the retinal pattern and note the proximity of one to the other. If the retina is attached, the mottled vascular choroidal pattern is seen clearly. If the retina is detached, its translucency masks the choroidal pattern and makes it appear blurred. Haziness of the media simulates this masking and often makes the diagnosis difficult. In such a case, contrasting a part of the fundus where the retina is definitely attached with the area in question frequently gives the answer by a rapid comparison of the two areas.

Another aid in determining whether the retina is detached in the early postoperative period is available if a scleral buckling operation has been performed. The change in contour of the retina as it goes over the buckle and suddenly dips down to the flat choroid posterior to the buckle is of value in determining attachment of the retina to the choroid (Fig. 1, above). If the retina simply tents off at the same level posterior to the buckle and does not dip down, it is evident that the retina is detached in this area (Fig. 1, below). This orientation is of special value when hazy media obscure other clues and prevent proper observation of detail.

Naturally, all of the other clues which aid in the preoperative diagnosis of retinal detachment may also be of help in the postoperative examination.

When direct ophthalmoscopy is used, reliance is commonly placed on the dioptric power necessary to see the retina. If more plus power is needed, the conclusion is drawn that the retina is detached. This interpretation is not reliable because of two common postoperative findings: 1. The sclera is frequently flattened in the area of diathermy, which increases the amount of plus power needed to view this area of the fundus with the direct ophthalmoscope. 2. The choroid is occasionally detached after retinal detachment surgery; this is especially frequent after a scleral resection. The misinterpretation of such a choroidal detachment is common and occasionally has resulted in needless reoperation because it was thought to be a retinal detachment recurrence.

If postoperative ophthalmoscopy shows the retina to be incompletely flattened, the relationship of residual subretinal fluid to the area of the retinal breaks and to the area of the surgically created diathermy barrier has to be evaluated. If the diathermy barrier is observed to be directly

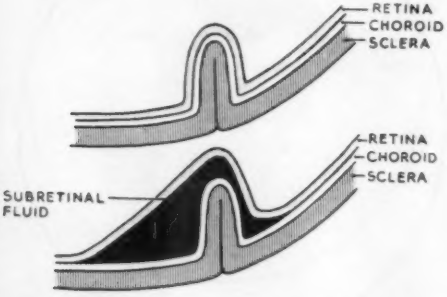


Fig. 1.—Above, retina attached to choroid as it accurately follows contour of buckle. Below, retina detached. It does not follow buckle contours, but rather tents off from crest of buckle.

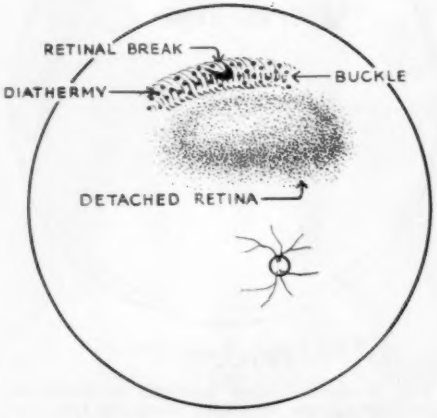
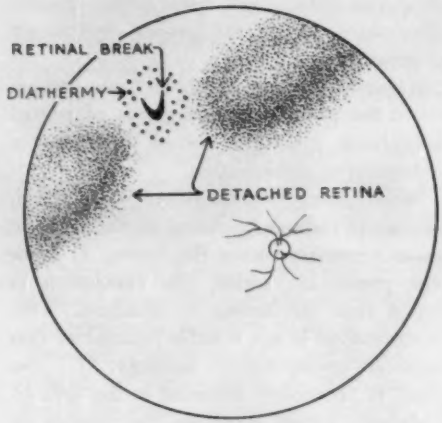


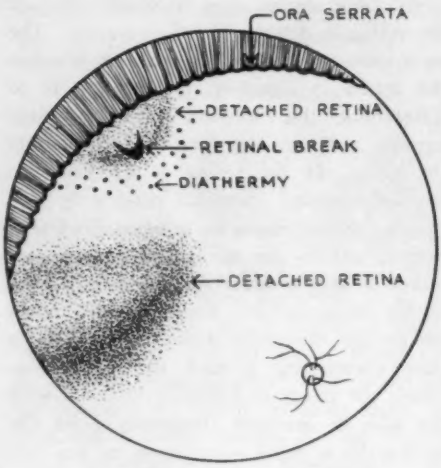
Fig. 2.—Retinal break against diathermized choroid of buckle. With the break sealed in this manner, the residual subretinal fluid posterior to the buckle will be absorbed, with final cure.



SUCCESSFUL

Figure 3

Fig. 3.—Retinal break surrounded by retina attached to diathermy barrier. The subretinal fluid elsewhere will be absorbed, with final cure expected.

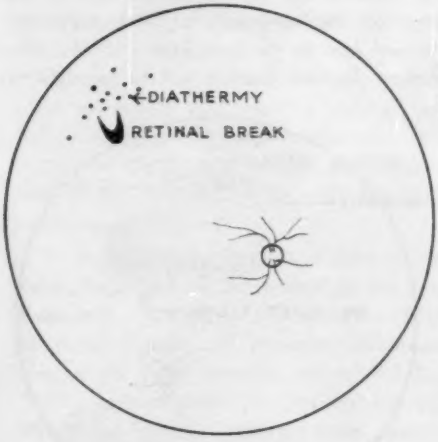


PROBABLE SUCCESS

Figure 4

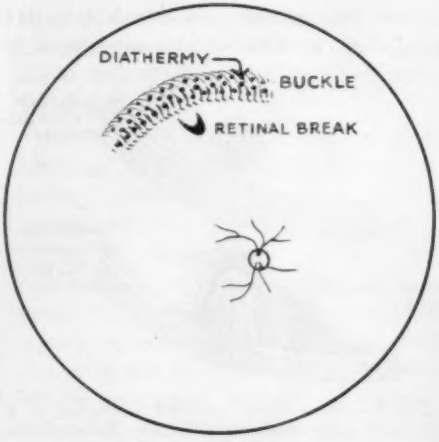
Fig. 4.—Retina attached to diathermy barrage posterior to retinal break and brought up to ora serrata. Even though the retinal break is not sealed, the diathermy barrier will probably prevent extension of the retinal detachment beyond it. The subretinal fluid trapped inferiorly will be absorbed, with probable cure.

under the retinal breaks, and includes their full length and width, the outlook is good if the retina is flat or almost next to the choroid in this region (Fig. 2). Also, if the diathermy barrier is posterior to the break the outlook is very good if the retina itself is next to the choroid over this diathermy and if the break is completely sur-



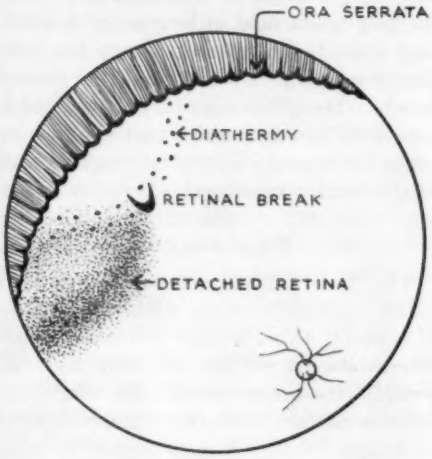
FAILURE

Fig. 5.—Retinal break posterior to diathermy. Even though the subretinal fluid has all been drained, the retinal detachment will probably recur soon.



FAILURE

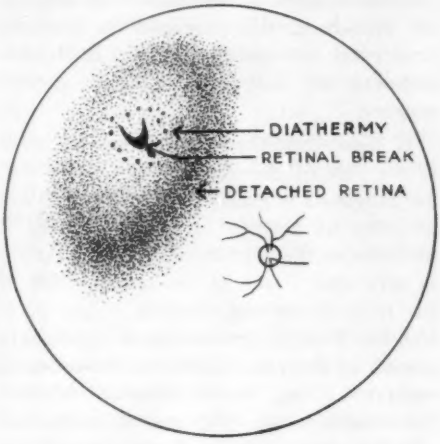
Fig. 6.—Retinal break posterior to diathermy of buckle. Although the retina is flat now, it will probably detach soon.



POSSIBLE FAILURE

Figure 7

Fig. 7.—Part of retinal break is just posterior to diathermy barrage. The chorioretinal scarring may extend posteriorly from the visible diathermy marks 1 to 2 mm. and seal the break. However, the margin of safety is very narrow, and the retina may well detach again.

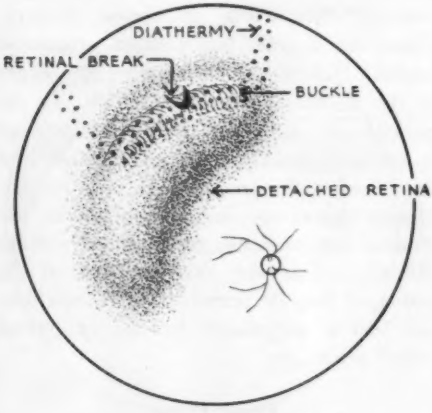


PROBABLE FAILURE

Figure 8

Fig. 8.—Diathermy correctly placed around the retinal break. However, the retina is not touching these diathermized choroidal areas, and therefore the detachment will not be cured.

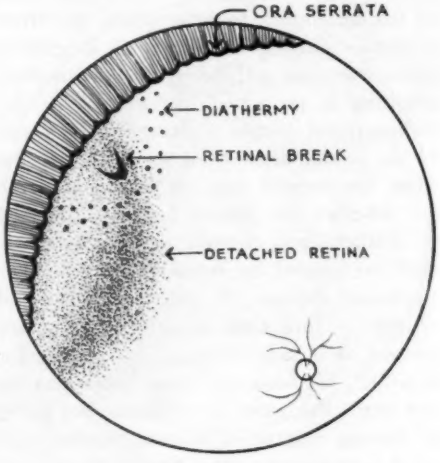
rounded by retina attached to the diathermy barrier (Fig. 3). Also, if the retina is attached to a diathermized arc of choroid extending posterior to the break and around it on either side up to the ora serrata the outlook is favorable (Fig. 4). Under these



PROBABLE FAILURE

Figure 9

Fig. 9.—Buckle and diathermy correctly placed under the retinal break. However, the retina is not against the buckle, and therefore the detachment will probably not be cured.



PROBABLE FAILURE

Figure 10

Fig. 10.—Diathermy well placed, but the retina is separated from the diathermy barrier inferiorly. This makes the effective barrier incomplete, and therefore it will not cure the detachment.

conditions, even if subretinal fluid is present elsewhere, the prognosis is probably very good for settling out and final reattachment of the retina without further surgery.

If these conditions do not prevail, even if the rest of the retina seems quite flat, the prognosis is guarded and the result will probably be failure. If the break area is posterior to the diathermy barrier, a failure is very likely, even if the retina is flat at the time of the examination (Figs. 5, 6, and 7). Even if the diathermy is correctly placed, as described above, if the retina is separated from the diathermized choroid the retinal breaks will not be sealed off and the retina will not become reattached (Figs. 8, 9, and 10).

It is of considerable value to note the progression or regression of the retinal detachment as determined by frequent sketches of the ophthalmoscopic picture. If the detachment continues to regress on successive sketches, the outlook seems to be good. However, if the detachment tends to increase in extent a reoperation is probably going to be necessary. It is important in deciding upon the increase or decrease of the detachment to differentiate this from a simple shifting of fluid due to gravity from one part of the retina to another, resulting in no actual increase in the detachment but simply a change in its place. If the retinal detachment seems to stay the same for several days, it is important to see whether the retinal break is attached to diathermized choroid or whether it is well surrounded by retina attached to diathermized choroid. If this is the case and if one is sure that no other breaks are present, it is safe to watch the patient for a while. If, however, these conditions do not exist, the retina is probably not going to become reattached without further surgical intervention. The sooner this is recognized and a reoperation is planned the better the eventual outlook for the eye.

Some types of retinal detachments settle very slowly postoperatively, and so more time can be given to watching them when the progress is slow, as long as ophthalmoscopy indicates that the diathermy has been placed properly in relation to the retinal breaks. The main type here is that of a retinal disinsertion, which may continue to settle for several weeks after surgery, with final retinal reattachment.

Pigmentation

The time of appearance of the pigmentation resulting from the diathermy barrage is variable. In most cases it appears somewhere between the 9th and 14th days. In general, the more intense the diathermy reaction the longer it takes for the pigment to appear. When it does appear it tends to develop first on the margins of the heavily diathermized spots. If the diathermy has been very light it may be seen first in the center of the diathermized spots. This is related to the fact that heavy diathermy will destroy the pigment epithelium, while light diathermy will stimulate its proliferation.

Hemorrhages

Small hemorrhages in the retina are common after retinal detachment surgery. These, as a rule, are without prognostic import. However, if the hemorrhage occurs in the macular area central vision may be permanently impaired. If the hemorrhage is extensive enough to break through into the vitreous, the prognosis is very serious. Hemorrhages can similarly occur in the choroid and, if small, are absorbed without difficulty. However, as with those in the retina, if they do occur in the macula they can lead to permanent decrease of central visual acuity.

Fixed Folds

The development of fixed folds of a star-shaped nature or of an equatorial circular distribution makes the prognosis less good, even though the retina appears to be flat postoperatively. However, one has to differentiate from these two types of fixed

folds a special type of small, thin, fixed folds often seen after any scleral shortening procedure. These are thin folds frequently related to the buckle area and appear almost as if a small piece of retina were pinched up in that region. They may be single or multiple. They appear to represent an excess of retina in relation to the immediate surface area of the inner surface of the globe, and they generally do not have any significant quantity of subretinal fluid beneath them. These folds are usually of benign prognostic import and do not affect the operative result as far as the attachment is concerned. They are usually innocuous unless one happens to go through the macula region, in which case the vision is disturbed even though the retina may remain attached. If vitreous or retina prolapsed through the choroid during the previous operation, a fixed funnel-shaped star fold of retina may be present at that point, which is pathognomonic of this serious accident. These folds may flatten out after several months if the retina remains attached.

Early Recurrence of Detachment

If the retina is completely flat at the conclusion of surgery and later detaches, it is very important to observe where the retinal detachment starts again. This may give an important clue to where the leak is and where it should be repaired. This early localization of the leak is frequently missed if one waits a week or so for the first postoperative examination by ophthalmoscopy.

Visual Fields

It may be stated here that visual-field examinations are not of too much value in determining early failure. It is not practical to determine early visual fields accurately, and they are not very reliable, especially if the beginning retinal detachment is in the periphery beyond the 50 to 60 degree range of the ordinary nasal visual field. However, if the visual field has once returned and then is lost a recurrence of the detachment is indicated.

Reoperation

The type of reoperation is dependent on the ophthalmoscopic findings during the

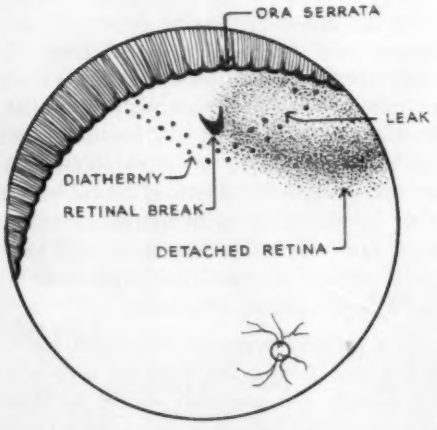


Fig. 11.—Diathermy barrier incomplete and leaking nasally. Further surgery is necessary to wall off the retinal break more effectively.

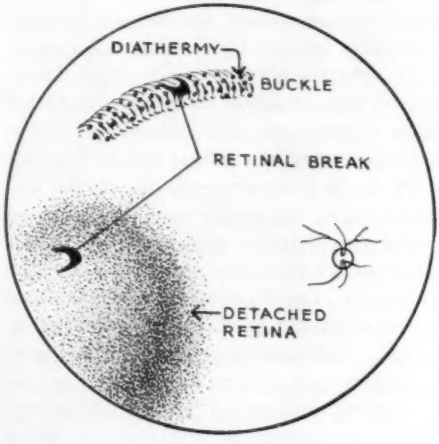


Fig. 12.—Buckle and diathermy well placed, with effective sealing of superior retinal break. The untreated inferior retinal break will have to be sealed by additional surgery to cure the detachment.

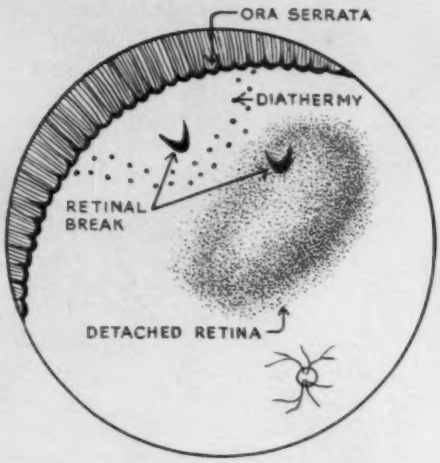


Fig. 13.—Superior retinal break effectively walled off. However, the additional break inferiorly will result in failure unless a reoperation seals it.

postoperative course. These cases can be fitted into several categories. If the leak occurs around the end anterior to the diathermy barrage or the buckle (Fig. 11), therapy is directed anterior to the diathermy barrage in the area of the break and also to better wall off the ends of the initial diathermy barrage up to the ora serrata.

If new or previously unnoticed breaks are present, attention should be directed to these breaks and they should be treated with diathermy or a scleral buckle (Fig. 12).

If the leak occurs posterior to the diathermy area, the retina may be completely settled except for an area of retinal detachment posteriorly which remains or increases (Fig. 13). Great pains should be taken to search diligently in this area for a break. Such a break may have occurred owing to penetration of the retina by one of the penetrating pins or even by simple intense diathermy causing a break in the retina without perforating it with a pin. In addition, it is possible that a break may either have developed postoperatively or, more likely, have been missed on the initial examination. In this case, therapy should be directed posterior to the diathermized area by (1) treating this new area with diathermy or (2) creating a buckle under this new break or (3) broadening a preexisting buckle posteriorly to include the additional retinal break. Of course, if it is seen that the initial diathermy did not encompass the original break properly additional diathermy or a scleral buckling should be performed to seal it off (Figs. 5, 6, and 7).

If the diathermy has been properly placed and yet the retina does not settle onto it, a scleral buckle in this area is indicated (Fig. 8). If a buckle is already present in correct position under the break, and yet the break will not settle onto it, the buckle may be made still higher by the use of an encircling polyethylene tube (Fig. 9). A vitreous implant may be of value in pushing the retina back to the diathermized choroid.

If fixed folds are present and no new breaks are found in the still-detached retina, it is probably of value to create a more extensive buckle by the use of an encircling polyethylene tube.

If the retina presents a picture of numerous stiff folds radiating out from the disc, which is at the bottom of the funnel of folds, so-called "massive vitreous retraction," the prognosis is practically nil for retinal reattachment. A rare case may be reattached by an extensive scleral buckle with an encircling polyethylene tube. In some cases the retina may be pushed back by a vitreous implant as a supplement to the aforementioned procedure.

If a primary operation has failed and it is felt that there is any hope for a cure of the patient, the operation should be done as soon as the failure is diagnosed. There is nothing to be gained by delay.

Department of Ophthalmology, University of California.

Retinal Detachment Surgery

An Enfolding of the Sclera

JAMES S. SHIPMAN, M.D., Camden, N. J.

In 1956 at the Academy of Ophthalmology and Otolaryngology Rolett presented a movie film entitled "Scleral Shortening: A New and Simplified Method of Use in Retinal Detachment." I saw this and was stimulated to try a modification of this operation. In my modification two incisions are made instead of one through the outer three-fourths of the sclera, with an island of full thickness of sclera between these. I wish to recommend this to you as a procedure for cases requiring more than the ordinary retinopexy but not such an extensive procedure as a resection of the sclera with insertion of a polyethylene tube.

The technique is as follows: The incision in the bulbar conjunctiva is made far enough away from the limbus to allow it to be reflected over the cornea as an apron-like flap to protect the cornea during the operative procedure.

The anterior edge of the conjunctival incision is caught with two twisted black nonabsorbable surgical (silk) sutures, and these are brought together and held with a Serafin clamp. The posterior conjunctival edge is caught with two twisted black silk sutures, and these are clamped separately with hemostats to the operative sheet, thereby retracting this edge away from the field of operation.

The rectus muscles are always temporarily tenotomized when they interfere with proper exposure. These are isolated and exposed; a whip stitch of 0000 chromic absorbable surgical (gut) sutures is inserted above and below, or on each side of the muscle, and this is then cut and the sutures are clamped with a Serafin clamp and laid aside.

A double-armed fixation suture of 0000 braided black silk is now inserted in the muscle stump, care being taken to include the sclera in each bite, and at least four bites are taken so that this will not pull out when the eye is rotated in various directions.

The entire sclera is then cleaned with a dry stiff cotton applicator and all bleeding is controlled with the diathermy tip. The various vortex veins are located and identified.

Another check is now made on the retinal hole or holes, which are localized by direct ophthalmoscopic examination, and a mark is made with methylrosaniline chloride (gentian violet) on the sclera, by an assistant, at the point where the light of the ophthalmoscope is transmitted.

This point on the sclera is then coagulated with a short Walker pin or the tip of the Walker electrode.

The area on the sclera for the incisions and the enfolding procedure is then outlined with methylrosaniline chloride. The anterior edge of this is usually 13 to 15 mm. from the limbus, and the posterior edge is 3 to 4 mm. behind this. The position and length of this area vary with the number and location of retinal tears and with the amount of shortening desired. The incisions are connected at each end and usually near the horizontal or vertical muscle insertions.

This area of enfolding or shortening should be placed close to or, if possible, back of the retinal hole or holes. It is then scored with a sharp knife of the surgeon's choice.

A row of electrocoagulations is then made well back of the equator and especially the tear. These coagulations are made with small Walker pins if the retina is well

elevated; otherwise, with the tip of the Walker electrode.

The incisions are now carried deeper through the outer three-fourths of the scleral coat. The anterior and posterior edges of the two incisions are then undermined for about 1 mm., leaving the strip of full thickness of sclera between.

These two areas of thin sclera and the strip of full thickness of sclera between are now touched very lightly with the Walker electrode tip. I then insert bone-waxed 0000 white silk mattress sutures from the anterior to the posterior edge and out again from posterior to anterior edge, so that the strip of full thickness of sclera will be between these edges and enfolded as the sutures are tied.

The ends of the sutures are left 4 to 5 in. long, and these are held taut by the assistant to prevent tangling.

More coagulations are then done with a short Pischel perforating pin between this area and the previously placed posterior coagulations or Walker pins, to evacuate the subretinal fluid.

These coagulations are carried all the way forward around the tips of the incisions up to the ora serrata, in order to seal off and make this entire area watertight. The Walker pins, if used, are then removed.

The mattress sutures are all carefully tied. If there has been sufficient evacuation of subretinal fluid, the edges will come together without too much tension. If this does not happen, a weak spot in the coagulated posterior thin sclera is found and the sharp tip of a lacrimal dilator is inserted just through the scleral fibers. Then the blunt tip is inserted through the choroid into the subretinal space and maneuvered slightly to evacuate more subretinal fluid, care being taken not to injure the retina or enter the vitreous chamber.

All remaining sutures are then tied, and the rectus muscles are resutured to or just behind their original insertions after the traction suture has been removed. The conjunctiva is then closed with a running whip stitch of twisted black silk.

Summary

The technique of a method of scleral shortening by enfolding of the sclera instead of resecting it is described.

Conclusions

I am convinced that more retinopexies should be done early by the average ophthalmic surgeon and fewer resections should be done by the so-called retinal specialists. If this practice is followed, the results will be much better, especially the "central visual" results. For borderline cases where there is a question as to which procedure to follow I recommend this scleral enfolding operation as described.

This procedure has the following advantages: 1. It is safer. 2. It is easier to do. 3. It does not require the insertion of a foreign body such as a polyethylene tube. 4. It does not cause so much reaction with late postoperative granulations, with discomfort to the patient. 5. It shortens the operating time.

I would warn against the recent trend to get detachment cases out of bed too soon. I still feel that every case of detachment surgery deserves at least two weeks of bed rest in a dependent position after surgery, if there are no contraindications.

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Surgery of Retinal Detachment—the Old Versus the New

JOHN W. HENDERSON, M.D., Rochester, Minn.

In October, 1951, at the annual session of the American Academy of Ophthalmology and Otolaryngology, a symposium on retinal detachment was presented. This symposium was of particular note because of the concise but complete coverage of such a broad subject, the renowned status of the speakers, and the large audience that attended the presentation. One of the speakers who participated in this symposium is now the president of this section, Dr. Dohrmann K. Pischel. Because of Dr. Pischel's particular interest in retinal detachment, the panel discussion of this subject today is very timely. I thought it appropriate, therefore, to reevaluate Dr. Pischel's remarks of 1951 in light of the developments that have occurred in the past six and one-half years and compare the clinical results obtained with the older technics and with the newer ones.

In the symposium of 1951 Dr. Pischel [1] discussed the treatment phase of retinal detachment and described a typical operative procedure. The salient features of the surgical manipulation that he described were the insertion of perforating pins in the immediate vicinity of the retinal break, the use of either nonperforating pins or surface diathermy over the area of the eyeball corresponding to the detachment, frequent ophthalmoscopic examination as a guide to the proper placing of the diathermy barrage, the technique for release of subretinal fluid, and the method of injecting air or saline solution into the vitreous chamber in those situations in which such a supplementary procedure was required.

Section of Ophthalmology, Mayo Clinic and Mayo Foundation. The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

In the intervening years since this symposium, the so-called scleral shortening techniques for the repair of retinal detachment have received wide publicity, particularly in this country. At almost every ophthalmic meeting in the past several years in which the subject of retinal detachment has been discussed, a new technique of reducing the circumference and volume of the eyeball by "scleral shortening" has been presented. In the informal discussions among "infrequent operators" (by infrequent operators I refer to those ophthalmic surgeons who perform only a dozen or so operations for retinal detachment a year and who are not always able to persuade their patients to consult an ophthalmic surgeon in one of the larger medical centers)—in these discussions which inevitably occur after such a meeting, the question is almost always asked, "Do you do scleral shortening operations?" If the ophthalmologist to whom this question is directed answers in the negative, the implication of such an answer is that he is not keeping abreast of the modern surgical approach to the problem. On the other hand, if the answer is in the affirmative, the surgeon realizes that his surgical technique has become outdated by the newer procedure just described.

As an interested listener at some of these hallway conferences, it seemed to me that the participants expressed a sense of frustration as to knowing which surgical procedure was proper. Furthermore, those who had not yet performed a scleral shortening procedure were bewildered as to whether to fold, invaginate, evaginate, slide, or buckle the sclera or bind the globe into the newest type of plastic girdle. The basic dilemma in these situations was whether

to continue with their usual surgical technique, at the risk of being considered old-fashioned, or to attempt the newer but more difficult scleral shortening procedures in the hope of improving the patient's result.

Of course, this rivalry between the new and the old is not peculiar to the scleral shortening approach to retinopexy but is a common accompaniment of all rapidly progressing scientific research. I dare say there will be twice as many scleral shortening procedures invented as now exist before the answer to these questions can be provided.

My advice to these kindred ophthalmologists is not to be fretful concerning their knowledge and application of these newer techniques but to remain with the classic technique of retinopexy, at least for the present. Although my own practice in respect to retinopexy can by no means be considered large, still I have had an opportunity over the past several years to try each of the newer techniques except the scleral girdle technique in several patients as primary, secondary, and sometimes tertiary procedures. Sufficient time has now elapsed to have formed some clinical impression of the results. It is my considered opinion that the incidence of six-month cures brought about by the various scleral shortening procedures is not significantly greater than the incidence of cures obtained by the less-complicated diathermy procedure, such as that detailed by Dr. Pischel at the 1951 symposium.

In the first place, the actual reduction in the volume of the globe induced by scleral shortening of whatever type has, clinically, not seemed as great as the reduction obtained by simple surface diathermy (electrocoagulation current). This impression is in agreement with the experimental work carried out by Scheie and Jerome[2] in 1949. Secondly, the application of diathermy to the adjacent choroid, as in the procedure of lamellar scleral resection, has not produced any greater benefit to the overlying detachment, in my judgment, than has the conventional insertion of perforating pins or electrodes. Third, among my patients there have been less postoperative reaction and faster convalescence with the standard diathermy procedure than with a scleral shortening procedure. Fourth and last, the technical skill required and the time consumed in performing one of these scleral shortening procedures constitute a serious disadvantage to the average busy ophthalmologist.

Therefore, I would caution those infrequent operators who are still in a state of wonderment as to the application and practicability of some of the newer methods of retinopexy not to give up the "old" for the apparent benefits of the "new." Instead, I would encourage them to reread Dr. Pischel's description of the "typical" operation, for I think that operation is still the best.

Mayo Clinic.

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The Importance and Employment of Diathermy in Retinal Detachment Surgery of Today

GRAHAM CLARK, M.D., New York

Despite the accent on the various aspects of scleral surgery today, the basic necessity in curing a retinal detachment is still to reestablish the integrity of the fluid barrier of the retina so that the form, function, and tissue relationships of the ocular tissues may be restored. Since neither the choroid nor the retina has the structural strength to be held to the other by sutures, we are forced to employ a method of creating our pressure seal which, we may say, employs its result as its means; that is to say, the retina and choroid must be held together by the pressure from the vitreous chamber, so that the exudate from the treatment reaction may effectively seal the retinal defect, but if the defect is not sealed we cannot reestablish the pressure factor. Fortunately, Nature is tolerant of our surgical blunderings and allows us to escape from this surgical dilemma, but if we are to improve our surgical results we must examine the elements of the creation of this essential fluid-pressure seal critically and strive to carry out our part with the maximum efficiency.

The only effective method we have yet devised to accomplish our part of this step is to cause a choroidal insult in the area around the retinal defect which will cause the choroid to exude an adhesive substance with sufficient strength through its fibrinous content to make a fluid barrier between the vitreous chamber and the subretinal space.

To do this, we employ a high-frequency electrical current, which, when it encounters the resistance of the tissues, will be converted, in large part, to heat, and a burn results. The choroid, being the most vascular of the tissues involved in this burn, will respond to the insult by pouring out a serous exudate. This mechanism was beautifully demonstrated in Dr. Pischel's paper of 1944.[1]

Investigation into the electrical side of this process has demonstrated two major variables in the reaction which, if ignored, can destroy its effect. The first lies in the electrical characteristics of the tissues involved, and the second lies in the thermal effect of the various currents employed.

The results of my experimental studies into the electrical characteristics of the ocular tissues are in essential agreement with the prior work of Cole and Curtis,[2] and Hemingway [3,4] and have been confirmed by the later work of Meyer-Schwickerath [4] and Irvine and Knoll.[5] All have found that the resistance offered by tissues to the flow of electrical currents is an infinitely variable impedance made up of the pure resistance of the substance plus a capacitive reactance from the cell walls and fluids. At any spot in any tissue the specific impedance to any given frequency of oscillating current can be determined, and it can be stated that, in general, the impedance drops as the frequency increases, but the variations between tissues and within the same tissue are so wide that the specific knowledge of these factors is of little practical use in surgery.

There are, however, certain basic factors active in the employment of electrosurgical currents which must be recognized and employed if this type of surgery is to be used with safety and optimum effect. First, we must remember that the thermal effect is obtained wherever the current, released from the electrode, meets significant resistance and that this effect is in direct proportion to that resistance. Of the three

tissues with which we are concerned in the treatment of retinal detachments—the sclera, the choroid, and the retina—the first and the last have the highest resistance. Thus, we are faced with the fact that, whereas we wish to have the heat effect in the choroid, that tissue is the one in which the least heat is generated from the current. The same high degree of vascularity of this tissue not only prevents the creation of heat by lowering its resistance but, owing to the rapid flow of blood, dissipates any heat formed very rapidly. This means that we must use a large amount of current for a considerable period of time to form the choroidal burns on which our treatment is based, and in doing so we endanger the retina, where the higher resistance makes this same current of greater thermal effect. Thus we see that we must be constantly aware of the electrical characteristics of these three tissues.

Secondly, we must know the tissue reactions of the three main types of electrosurgical current that we employ: (1) the fulgurating, (2) the coagulating, and (3) the cutting currents. The first is the blue spark that jumps from the electrode to the tissue simply because the tissue is at a lower potential than the electrode and offers an unobstructed path. This arcing, monopolar application we call desiccating, because most of the electrical energy is given up in the spark as light and sound and only enough reaches the tissues to boil the tissue fluids and explode the cells by their own steam. There is little vascular damage resulting, and the healing is characterized by a lack of scar formation. Also, the effect is, of necessity, purely surface effect. The second, or coagulating, current is produced by a spark-gap oscillator and requires that the tissue be in the circuit. The effect is gained by condensing the current through the small tip of an electrode and picking it up by a broad plate. Because the oscillating of the voltage across a spark gap tends to damp itself, the average voltage output is relatively low and flows constantly through the tissue, creating a high heat which results in coagulation and actual carbonization. The third, or cutting, current is the product of an oscillating tube and puts out a constant high-peak voltage wave. So high is this peak voltage that it blasts the tissue instantly at the point of contact and breaks the circuit before any deep heating results. A narrow pathway is therefore blasted by the electrode, which resembles a knife cut, with little effect to any tissue which does not come in direct contact with the electrode.

Thus we see the three effects: low surface effect from the first type of current, widespread penetrating heat from the second, and local heat at the point of contact with a knife-like action from the third.

With proper knowledge of these factors we can utilize the process which we loosely term "diathermy coagulation" to create a fluid-tight seal around the retinal hole which caused the detachment and, with the subretinal fluid removed, effectively cure about 60% of the detachments. These are, of course, uncomplicated detachments in which no mechanical factor acts to prevent the retina from returning to its normal position.

In a series of 125 consecutive cases recently examined after a minimum follow-up period of six months, it was found that diathermy coagulation alone had been employed in 52% of the cases, with 93% successful results. With so much talk of scleral surgery, I think it is important to note this reevaluation of the simpler method, for not only is it highly effective in a high percentage of cases but it also forms an essential element in the treatment of complicated cases, where additional procedures must be used.

From these facts we have a method of surgery which combines many elements of previous operations to create one operation which has great flexibility in the results that may be obtained. First, it recognizes that in the application of diathermy the sclera represents only an unwanted barrier. A sclerotomy incision is carried down to the inner layers, where the dark choroid shows

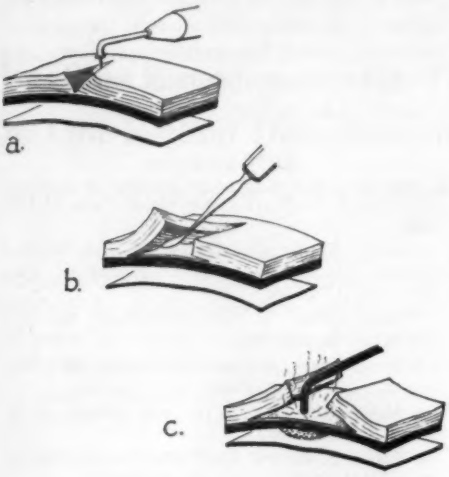

Figure 1

through as an even pale gray coloring (Fig. 1). This sclerotomy incision is placed to correspond to the line in which the major chorioretinal adhesion is desired to effectively seal off the retinal defect. The lips of the sclerotomy incision are then undermined to the extent that the choroidal reaction is desired in breadth. Light diathermy is then applied to the dry base of this broad sclerotomy incision through the blunt tip of a fine electrode until a continuous band of choroidal reaction is observed within the eye where it is desired. The subretinal fluid may be drained before or after the application of the diathermy current, but this should be done by perforations outside the sclerotomy incision and care should be exercised not to soften the globe excessively, lest the heat of the diathermy current cause excessive but temporary shortening due to shrinkage of the remaining scleral lamella.

Once the desired choroidal reaction is obtained, the situation of the retina, with its subretinal fluid drained, is observed and a final decision is made as to whether scleral shortening or buckling is needed. If the retina appears to be settled easily in place, with no evidence of traction, the sclerotomy wound is closed by simple approximation of the lips of the wound by a running or interrupted suture (Fig. 2). If some reduction in area and volume is seen to be indicated, the wound edges are drawn firmly together. The effect of a 2 to 3 mm. scleral resection may be obtained in this manner at any point or throughout the length of the wound. If a buckle seems indicated, firm suturing with a horizontal mattress suture will produce a surprisingly high choroidal roll within the eye, with, of course, the line of reaction riding on its crest.

In the suturing of the sclera a third advantage will be noted, in that the scleral lips have not been damaged by the diathermy current and have, therefore, their maximum strength.

Should it be desired, a polyethylene tube or fascia lata strip may be placed in the bed of the sclerotomy incision before closure and an implant buckle may be thus obtained.

The helpful features of this procedure can be summarized as follows: 1. The diathermy current is applied almost directly

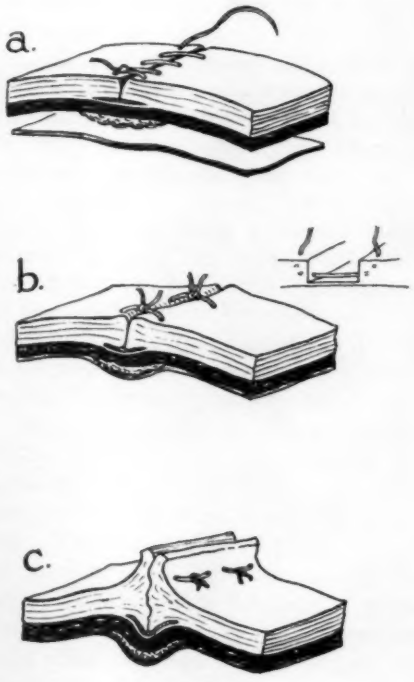

Figure 2

to the choroid and can therefore be used in minimum amount with maximum and uniform effect. 2. The line of reaction and, therefore, the chorioretinal seal are continuous, which minimizes the possibility of fluid leaks. 3. The procedure is flexible and can be varied at any point to meet any needs observed. 4. The diathermy burn does not involve the sclera and makes for greater strength in the suture line and leaves a minimum of scleral weakening which may limit a second procedure if reoperation is needed.

Summary

The importance of the employment of diathermy in retinal detachment surgery is accented, and the thermoelectric characteristics of the various currents and tissues are outlined. A new modification of the surgical approach, which has greater specificity and flexibility as its chief features, is outlined.

635 W. 165th St. (32).

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Further Experience with Vitreous Implants in Old Retinal Detachments

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The vitreous implant is not to be confused with the vitreous transplant. The implant is a technique for adding new vitreous to cases of retinal detachment, while the vitreous transplant is an exchange of clear vitreous for cloudy or bloody vitreous.

The basic premise of the use of vitreous in retinal detachment was that it hydraulically could pump the retina back in place, but so could air or saline. The second premise for its use was that vitreous seemed to be what kept the retina normally attached in the first place, for the retina has no attachments between its two extremities—the ora serrata and the disc. The final premise is that vitreous is the normal inhabitant of the vitreous chamber. Therefore, replacement by more vitreous seemed the logical procedure. This has been well expressed by Dr. Graham Clark, who feels that the retina is a membrane in the midst of a hydraulic system of the eye that does not permit its normal tenant (vitreous) to escape but may lose air or saline.

With that background, sterile donor vitreous—as aspirated from eyes donated to the National Eye Bank—was implanted in old retinal detachment cases that had failed with the usual techniques of retinal surgery.

The technique of a vitreous implant is a relatively short addition to the standard diathermy procedure, and both depend on the integrity of the diathermy to build a solid waterproof dike around all retinal leaks. It must be stressed that unless the retinal tears are sealed all modern-day detachment surgery fails.

The vitreous implant technique consists of making a 3 to 4 mm. incision through the sclera down to but not into the pars plana, 8 mm. back and at right angles to the limbus. Then a 00000 nylon (Dermalon) mattress suture with the arms 1.5 mm. apart is placed edge-to-edge across the incision. A second nylon mattress suture, with the arms 4 mm. apart, is placed edge-to-edge across the scleral incision but in the opposite direction. Thus, there are two mattress sutures opposing each other, and by their counterpull they can make a watertight closure. The usual diathermy and subretinal drainage is then done. After this, the surgeon returns to the prepared vitreous planting site.

The base of the planting site is touched lightly with diathermy to reduce the chance of bleeding; then, with an assistant holding the nylon mattress sutures, an 18-gauge needle on a syringe containing donor vitreous is inserted into the eye. The eye pressure is built up slowly to approximately 50 mm. (Schiøtz), and this is held for two minutes and then released to approximately 30 mm. (Schiøtz) as the needle is withdrawn and the suture triple-tied. A ring of nonperforating diathermy is then placed around the vitreous planting site.

What have been the experiences with the implantation of vitreous in old retinal detachments? We say *old* to mean those that have been operated on unsuccessfully before. No new or fresh detachment cases are considered in this study because we believe that an honest judgment as to the results of the procedure could be learned only when the usual retinal surgery had already failed.

TABLE 1.—*Preoperative Complications in 105 Consecutive Vitreous Implants, All Previous Surgical Failures*

Complication	Operations, No.	Success, %
Total detachment	60	33.3
Vitreous bands	20	25.0
Aphakia	45	27.0
Previous scleral surgery	15	53.3

TABLE 2.—*Visual Results in 105 Consecutive Vitreous Implants, All Previous Surgical Failures*

Vision	Per Cent	
20/15 to 20/40	19	81
20/50 to 20/100	35	
20/200	27	
Less than 20/200	19	
	100	

A consecutive, not selected, series of 105 old detachments were operated upon with the vitreous implant. The preoperative complications are shown in Table 1. These cases included one to five previous surgical failures of standard diathermy or scleral techniques.

What were the results for our patients? No amount of conversation will ever convince a patient that "anatomical reattachment" with poor or no light perception is satisfactory. The basic criterion of successful detachment surgery is seeing.

The visual results in this series of old retinal detachments are shown in Table 2.

One of the first fears in the use of human vitreous in detachment surgery was the fear of an infection. The potential infective properties of the donor vitreous have thus been of particular interest. In 1956 at the American Academy of Ophthalmology one of us (D. M. S.) stated that human vitreous could be deliberately contaminated and then it would become sterile. This statement has been rightfully contested. So we have explored it further. Recently our stored vitreous at the National Eye Bank was checked. There we kept it in a household refrigerator at 40 F—the same temperature as many home refrigerators, and we have human vitreous that has been in storage for 11 years without visible change; probably one of the longest human "bank" storages.

One of our residents at Manhattan Eye, Ear and Throat Hospital has been delib-

Fig. 1.—Blood agar plate contaminated with hemolytic staphylococci. Comparative inhibition circles shown around vitreous (bottom), tetracycline (left), and an ointment containing polymyxin B and bacitracin (Polysporin) (right).

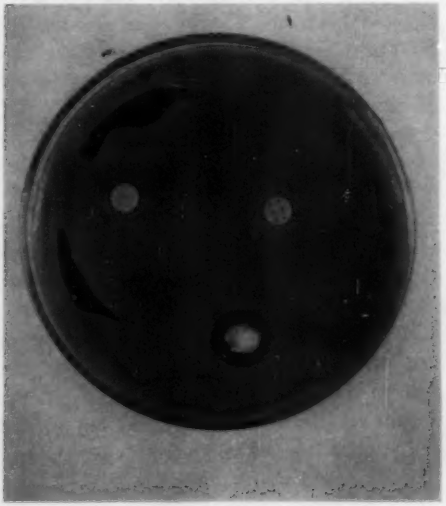
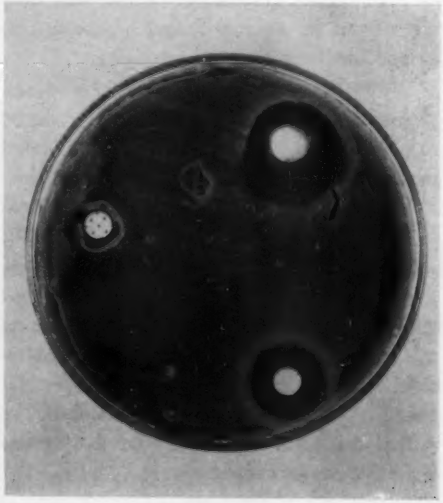


Fig. 2.—Blood agar plate contaminated with Hemophilus aegyptius. Comparative inhibition circles shown around vitreous (top), tetracycline (bottom), and Polysporin (left).



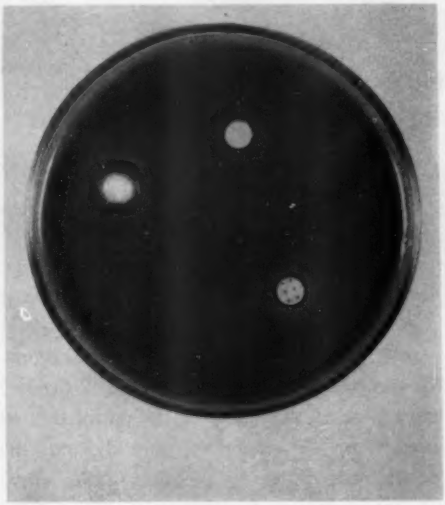


Fig. 3.—Blood agar plate contaminated with Pseudomonas aeruginosa. Comparative inhibition circles shown around vitreous (left), tetracycline (top), and Polysporin (bottom).

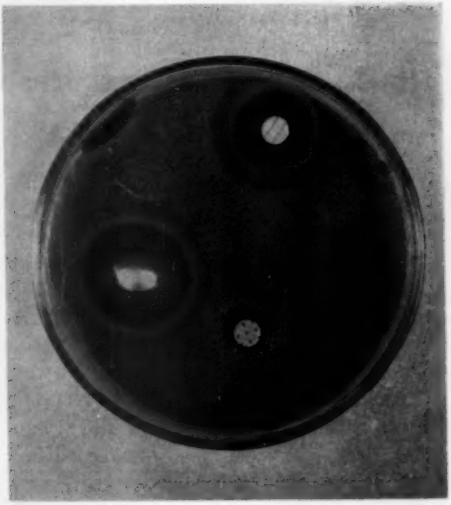


Fig. 4.—Blood agar plate contaminated with Proteus. Comparative inhibition circles shown around vitreous (left), tetracycline (top), and Polysporin (bottom).

erately contaminating this stored human vitreous. One of us (J. L. B.), as one part of his work, used the inhibition plate technique similar to that used in the early penicillin research. In this method he contaminated blood agar plates with various bacteria and incubated them at 37.5 F for 48 hours, till the growth of bacteria was visible. He then drilled a well in the agar holding 0.2 cc. and filled it with refrigerated donor human vitreous. As a comparison he placed two pellets each impregnated with one of two accepted antibiotics on the same blood agar plate. The results with four bacteria that are problems in eyes are shown in Figures 1 to 4.

It is immediately apparent that refrigerated human vitreous inhibits the growth of these bacteria distinctly more than the discs impregnated with antibiotic.

These surprising results, of course, suggest more questions than answers. However, they seem to show why we have not had a problem in using refrigerated human vitreous in old retinal detachments.

Therefore, it is stressed that the use of the vitreous implant in retinal detachments, when indicated, results in a satisfactory percentage of "physiologically attached" retinas.

140 E. 54th St. (22).

Diathermy or Scleral Resection

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Diathermy and scleral shortening operations are both effective for the cure of retinal detachments. The principle of sealing the hole and draining the subretinal fluid to allow reattachment of the retina can be accomplished by either procedure. As a matter of fact, both operations have a very similar effect on the eye: namely, shortening of the sclera, reduction of the volume of the eye, and closure of the retinal hole with diathermy.

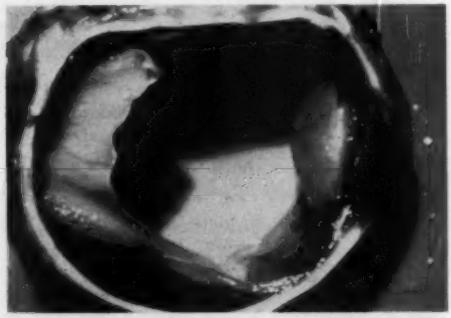


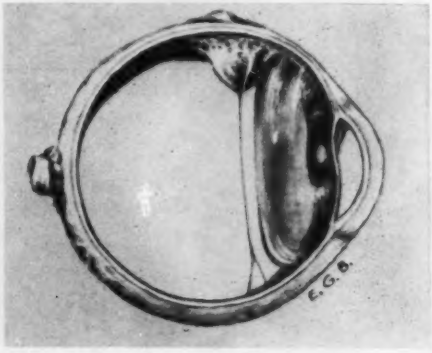
Fig. 1.—A photograph of a globe removed 10 days after diathermy operation. The upper half of the globe shows flattening of the sclera in the treated area.

Fig. 2.—A photomicrograph of a section taken from the globe in Figure 1. The upper half of the sclera is flattened and reduces the volume of the vitreous. Such flattening of the sclera produces at least 4 mm. of scleral shortening.

When a retinal detachment is treated by means of nonperforating intrascleral diathermy, a choroidal scar is produced that will close the retinal hole and create a firm chorioretinal adhesion sufficiently strong to permanently reattach the retina. In the course of treatment there is marked shrinkage of the sclera of the entire treated area. This shrinkage not only shortens the sclera but reduces the volume of the vitreous cavity (Figs. 1 and 2). Both structural changes are desirable in order to facilitate a reattachment of the retina.

Oftentimes the shortening of the sclera is temporary, but this may be no disadvantage. Once there is a broad chorioretinal adhesion that seals the hole in a water-tight scar, the retina can stretch to accommodate the gradually expanding sclera. It is not the stretching of the sclera that causes a retinal detachment but the traction from within. Even large staphylomata do not produce detachment unless there is some pull on the retina (Fig. 3).

Fig. 3.—An artist's drawing of a globe with an equatorial staphyloma. No detachment is present, but the vitreous is adherent to the atrophic chorioretinal scar within the staphyloma.



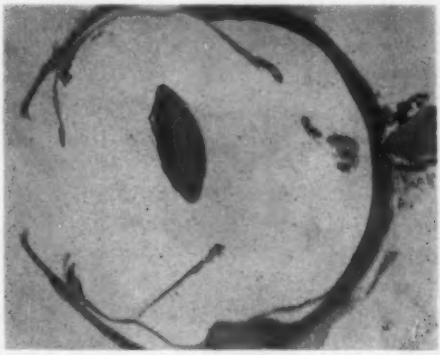


Fig. 4.—A photograph of a globe made 12 days after scleral resection. Inward buckling of the sclera is shown below.

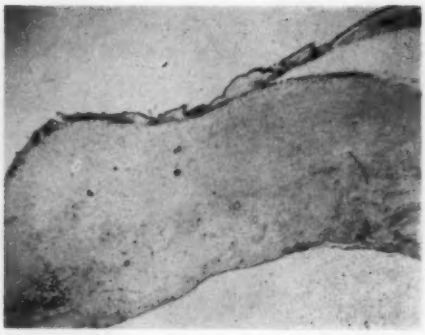


Fig. 5.—High-power view that shows the chorioretinal adhesion along the scleral ridge.

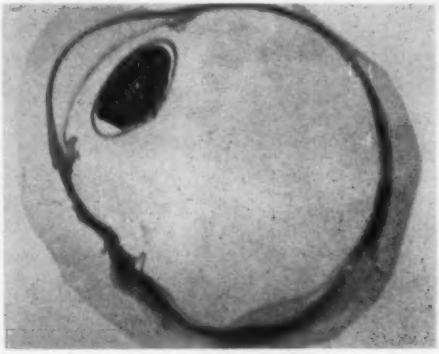
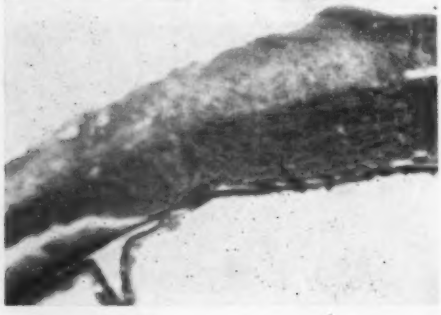


Fig. 6.—A photograph that shows a slight residual flattening of the sclera three months after scleral resection. The scleral ridge has disappeared.

Fig. 7.—A photomicrograph that shows the area of scleral resection. The scleral ridge has disappeared.

Fig. 8.—A photomicrograph of a section through a scleral buckle. The section was made from an eye removed immediately after operation. (Photograph provided by Dr. William G. Everett.)

Fig. 9.—A photomicrograph taken of a section through a scleral buckle 10 days postoperatively. (Photograph provided by Dr. William G. Everett.)



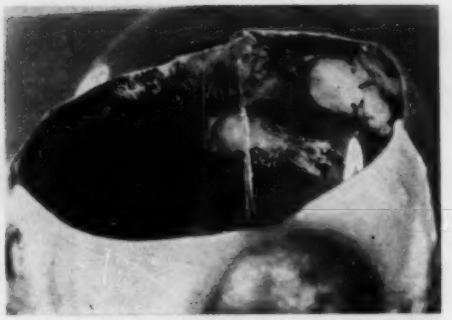


Fig. 10.—A photograph showing a dense vitreous strand adherent to an area of chorioretinitis. Such traction has not produced a retinal detachment.

Fig. 11.—A photograph of a normal globe. Marks are placed 5 mm. apart.

Scleral resection, whether it be infolding of tissue or an outward buckling, creates a shortening of the sclera along with reduction in the volume of the vitreous cavity. This operation alone will not execute a cure but depends on diathermy to produce a scar that will seal the hole and effect union between the retina and choroid. The infolding of the sclera produces a ridge to which the retina can become adherent (Figs. 4 and 5). In time this ridge flattens out to form a dense chorioretinal scar. The initial shortening in a scleral resection is probably not permanent, but the eye gradually resumes its normal shape and size (Figs. 6, 7, 8, and 9). This, also, need not be a disadvantage. A broad base of chorioretinitis can often withstand considerable traction from the vitreous (Fig. 10).

In order to compare the effects of diathermy with scleral resection, freshly enucleated eyes were measured and subjected to either diathermy or lamellar scleral resection. Application of diathermy over an area slightly greater than one quadrant caused a reduction of 1.3 cc. in volume, as measured by water displacement (Figs. 11 and 12). There was more than 3 mm. of shortening in a 5 mm. band of treatment (Fig. 13). Such treatment properly placed is very favorable for a reattachment if the condition of the retina and vitreous are such that traction no longer exists.

In the second group a 3 mm. lamellar scleral resection was performed over an area approximating one-third of the circumference (Fig. 14). Following this procedure there was a reduction in volume of

Fig. 12.—A photograph of the globe shown in Figure 11 after an intrascleral diathermy barrage has been applied to the sclera. Note the marked flattening of the globe.

Fig. 13.—A photograph of the globe shown in Figure 11 after the sclera has been treated with intrascleral diathermy. Three millimeters of scleral shortening was produced within a five-millimeter band of treatment.

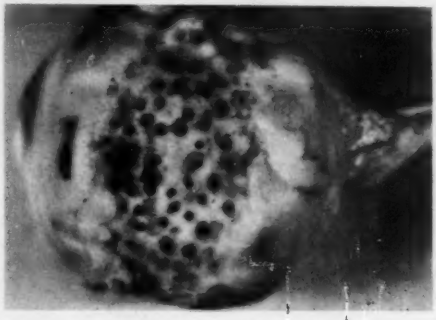


Figure 14

Fig. 14.—A photograph of a normal globe with marks spaced 5 mm. apart.

Fig. 15.—A photograph of the globe shown in Figure 13 after a 3 mm. lamellar scleral resection was completed. Three millimeters of scleral shortening resulted from the procedure.

Figure 15

Fig. 16.—A photograph of the normal globe shown in Figure 13 after a lamellar scleral resection was completed. Note that there is no flattening of the sclera.

Fig. 17.—A photograph of an eye that shows a dense vitreous strand.

Fig. 18.—A photograph of an eye with a shrinkage of the vitreous and traction on the retina at a point of retinovitreous adhesion. A reexpansion of the vitreous body may not only cushion the retina but relieve the traction exerted by the vitreous strand.

Figure 17

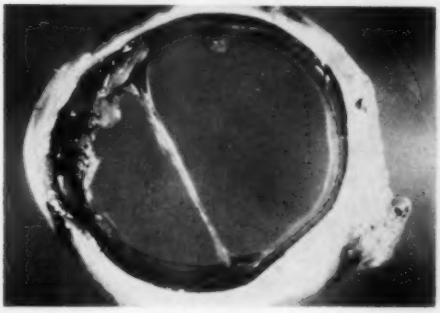
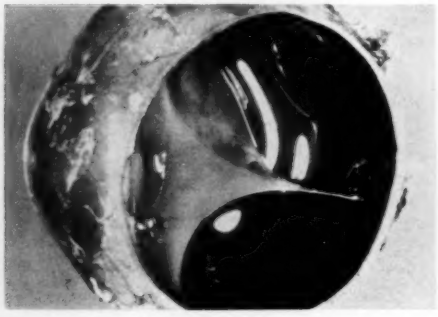


Figure 18



0.5 cc. and the actual shortening was slightly more than 3 mm. (Figs. 15 and 16). Some of the shortening was the result of the diathermy applied to the bed of the resected area. No additional diathermy was applied to these eyes, in order not to complicate the true effect of the scleral resection.

In view of the mechanism that causes the great majority of retinal detachments, it appears more logical and fundamental to treat the vitreous as well as the retina. The implantation of vitreous after the holes have been sealed with diathermy amplifies the effect of the treatment. Many dense vitreous strands completely disappear after the use of vitreous (Fig. 17). A reexpansion

of the vitreous body may simplify the problem to where simple diathermy is the operation of choice (Fig. 18), thus obviating a more complicated and difficult procedure.

108 E. 68th St. (21).

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The Application of Ultrasonic Locating Techniques to Ophthalmology

II. Ultrasonic Slit Lamp in the Ultrasonic Visualization of Soft Tissues

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Introduction

This is a preliminary report of the visualization of the interior of the light-opaque eye and the retro-ocular areas by pulsed ultrasonic echographic methods. Non-radio-opaque foreign materials, such as wood and plastics, may also be visualized, as well as soft tissue pathology.

At present no other method can yield the information obtained by the technique to be described. A comparison of the visual appearance of a normal beef eye, the x-ray appearance, and the sonic appearance graphically illustrates this contention (Fig. 1). The x-ray demonstrates only the gross outline of the eye. The ultrasonogram reveals a cross section of the internal structure of the eye equivalent in detail to a low-power photomicrograph. Serial ultrasonic tomograms (Figs. 13 to 21) yield a composite picture of the eye at all levels without in any way altering the tissues.

Precise direct measurement of the depth within the tissue is possible with this device. This dimension could not heretofore be directly measured short of surgical exposure.

In the past, soft tissue structures within the body could be visualized only by surgical exploration and soft tissue x-ray techniques with the use of the contrast media.

Disadvantages of X-Ray Techniques

X-ray visualization of soft tissue possesses inherent disadvantages because the

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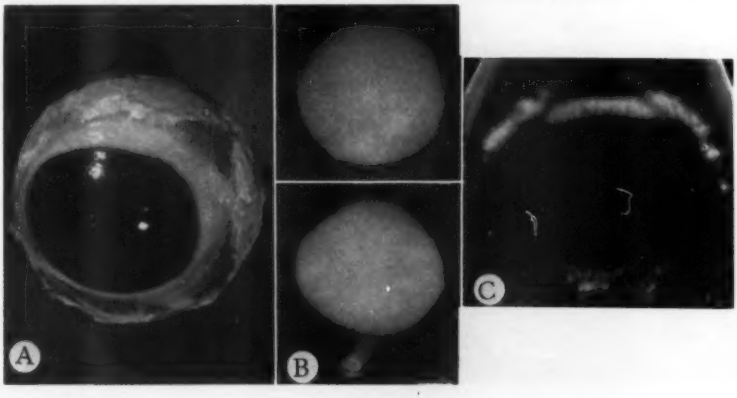
Fig. 1.—A comparison of the appearance of the beef eye grossly, by x-ray, and ultrasonographically. *A*, gross appearance. *B*, x-rays, anteroposterior and lateral. *C*, ultrasonic tomograph.



Summary of Advantages of Ultrasonic Visualization

Advantages of Ultrasonic Visualization of Soft Tissues	Disadvantages of X-Ray Visualization of Soft Tissues
1. The soft tissues may be visualized directly, without the use of contrast media; the detail is equivalent to that of a low-power photomicrograph	1. Soft tissues have uniform density to x-ray; contrast media are required, but the detail fails to equal that obtained by ultrasonic visualization; contrast media are irritating and possess toxic side-effects
2. Safe at the levels used for visualization; no immediate, cumulative or delayed effects	2. Danger of x-ray exposure and cumulative effects
3. Depth and angular location can be directly measured, without markers	3. Markers are required
4. Most forms of foreign materials may be visualized and localized	4. Many substances possess the same x-ray density as the soft tissues in which they are embedded and cannot be visualized
5. Visualization and localization may be performed in any part of the eye or orbit	5. Radioisotope localization and identification of tumors is dependent upon their anterior location and selective uptake

soft tissues of the body exhibit a uniform density on x-ray examination. Even the best soft tissue x-ray techniques demonstrate only gross soft tissue structure (Fig. 1).

Contrast media, such as iodides, barium, and air, have been used to obtain a greater density differential and delineate the finer defects in soft tissue structure. At best, these fail to provide the detail available by ultrasonic visualization.

Such media used intraorbitally have proven to be irritable.[1] Walsh[2] has reported numerous complications following carotid angiography.

Tumor localization by radioisotope-uptake may be unsatisfactory because lesions of the posterior segment of the eye are inaccessible to the Geiger counter and/or the tumors fail to exhibit a selective uptake of the radioisotope.[3]

All forms of x-ray subject the eye and body to the hazard of exposure, as well as the cumulative and delayed action of x-ray.

Advantages of Ultrasonic Visualization

The soft tissues themselves can be "visualized" by high-frequency sound waves. Thus, the need for contrast media is eliminated. Ultrasonic waves are harmless at the energy levels used to visualize soft tissues. Doses 1000 times in excess of those used in the ultrasonic locator are without demonstrable effect upon the tissues at reduced peak voltages. There is no known delayed or cumulative damage from ultrasonic radiation, such as may follow x-ray. All portions of the globe and orbit may be reached. Selective uptake by various tissues is not a problem, but differences in the reflective and absorptive properties of tissues in relation to ultrasonic waves may actually facilitate the differential diagnosis of tissues. (This phase of ultrasonic differentiation will be discussed in another paper.)

Principle of Operation

An ultrasonic locator is essentially a slit lamp in which pulsed high-frequency sound waves have been substituted for the light source. A microphone is substituted for the microscope. The entire assembly scans the eye so as to obtain a cross sectional view (i. e., a tomogram) of the tissue being studied. In practice, considerable simplification of the apparatus is achieved by combining the sound-generating and -receiving source into one unit, called the transducer.

Analysis of Operation

Figure 2 is a block diagram of the major units of the ultrasonic locator. An electrical pulse is produced by the generator (*A*). This pulse causes the crystal to produce a pulse of high-frequency sound waves (*B*). The latter must be coupled to the eye by a liquid to prevent their absorption by the air.

How Tissues Are Visualized

Figure 3 is a representation of what happens at the eye when both light and sound are used.

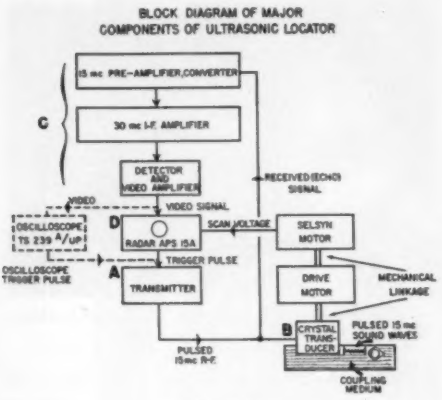


Figure 2

Fig. 2.—Block diagram of major components of ultrasonic locator. *A*, pulsed 15 mc. R-F current generated by transmitter. *B*, crystal converts electrical energy into sound. Sound waves travel through water and strike the tissue. Reflected sound waves received back at crystal, which reconverts the sound back into electrical impulses. *C*, electrical impulses are amplified by receiver. *D*, radar receiver converts electrical impulses into blobs of light of proportional intensity and correct position.

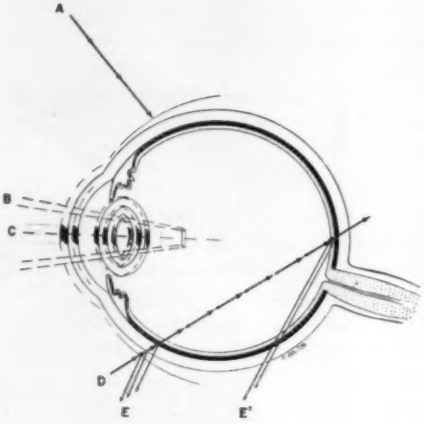


Figure 3

Fig. 3.—A comparison of the visualization of the eye by the light and sonic slit lamps. *A*, light incident upon the heterogeneous surface of the sclera is absorbed, diffused, and reflected so that only the surface of the sclera can be seen. *B*, light incident upon the homogeneous cornea is transmitted into the depths of the eye. *C*, as light passes through zones of optical discontinuity, i. e., different indices of refraction, a reflection occurs at each interface. *D*, high-frequency sound waves can penetrate the soft tissues of the body regardless of their optical properties. *E* and *E'*, as the sound waves pass through tissues possessing different acoustic impedances, reflections are set up at each interface. These reflections are detected by the receiving crystal and converted into electrical impulses. The latter are amplified and then converted into light of varying intensities, so as to form a picture on the face of the cathode-ray tube.

When the sound pulse (Fig. 3*D*) strikes any surface of the eye, a portion of the sound wave is reflected and the remainder is transmitted to the deeper structures of the eye. As the sound waves pass through tissues of different acoustic impedances a portion of the sound energy is reflected (Fig. 3*E* and *E'*) and the remainder is transmitted onward, until the energy is totally absorbed. A reflected wave is set up at each interface. An identical phenomenon occurs optically as the light beam of the slit lamp traverses tissues whose index of refraction differs (Fig. 3*B* and *C*). The outstanding difference is that the structures which are opaque to light, such as the sclera and the retro-ocular areas, are transparent to sound.

Methods of Presenting the Information

The reflected sound waves are picked up by the microphone, which converts the

Fig. 4.—Formation of the ultrasonogram. *A*, the appearance of the front and rear surfaces without scanning (trace off). *B*, appearance of front and rear surfaces with a slow scan (trace off). *C*, formation of the ultrasonogram with use of a rapid scan (trace on).

sound energy into electrical impulses (Fig. 2*B*). The electrical impulses are amplified (Fig. 2*C*) and then converted into blobs of light on an oscilloscope in which the intensity is proportional to the intensity of the reflected sound (Figs. 2*D* and 4*A*).

To obtain a cross sectional view of the tissues under study, the transducer is moved across these tissues (Fig. 4*B*). A mechanical-electrical linkage system correlates the position of the electrical trace of the oscilloscope with that of the transducer so that a picture, or sonogram, results. Figure 4*C* shows the formation of the ultrasonogram; the outlines can be seen dimly, and the trace line is prominent.

Technique of Using the Sonic Slit Lamp

Experimental studies are conducted by submerging the tissues and transducer in a tank of saline or water (Fig. 5). Examination of patients is conducted by mounting the transducer on an adjustable assembly such as is shown in Figure 6. The patient places his face inside a rubber mask built into the side of the tank. The tank is filled with isotonic saline.

Fig. 5.—Detailed view of scanning system. *A*, Selsyn motor, for synchronous positioning of transducer and sweep of cathode-ray tube. *B*, drive motor. *C*, transducer, mounted at the end of the shaft of the Selsyn motor. *D*, tank for submerging specimens and transducer.

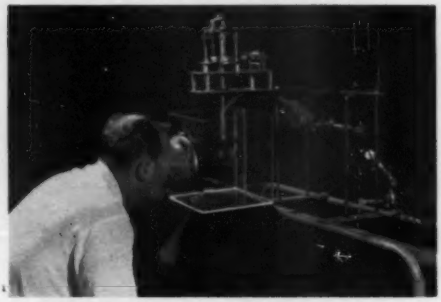


Fig. 6.—Apparatus used for the clinical examination of patients.

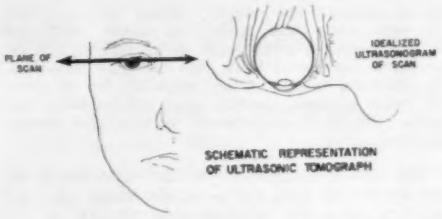


Fig. 7.—Schematic representation of an ultrasonic tomogram. Serial tomography is performed by scanning the eye at succeeding levels.

Orientation

The schematic diagram (Fig. 7) facilitates the understanding of the succeeding ultrasonograms. The ultrasonogram represents a horizontal section, or planigram, through a level of the eye. It is similar to a slit-lamp section, except that only tissues in the section are visualized. The remainder of the eye can only be visualized by performing serial planigrams at other levels.

Fig. 8.—Gross appearance of the eyes of the patient. Note the haziness of the cornea and the hyphema of the right eye.

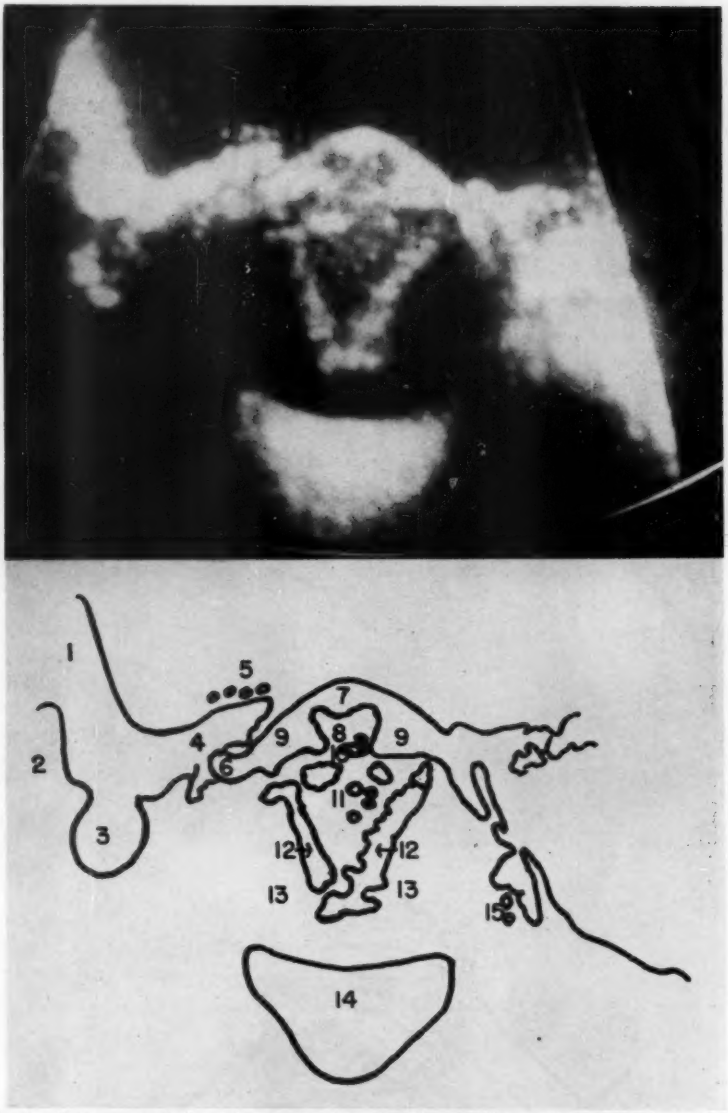


Fig. 9.—Echogram of the right eye, in situ, of patient in Figure 8. *1*, nose; *2*, nasal cavity; *3*, nasolacrimal sac; *4*, lid; *5*, cilia; *6*, caruncle; *7*, cornea; *8*, anterior chamber containing blood; *9*, ciliary body; *10*, iris; *11*, vitreous hemorrhage contained wholly within the totally detached retina; *12*, totally detached retina; *13*, clear subretinal fluid; *14*, sclera and retro-orbital fat.

The term "sections" is thus used in the same sense as in "slit-lamp section." An ultrasonic tomogram or planigram would be a more descriptive and accurate term. The ultrasonograms appear as compound coronal-sagittal sections, as viewed from an anterior position.

Fields of Application

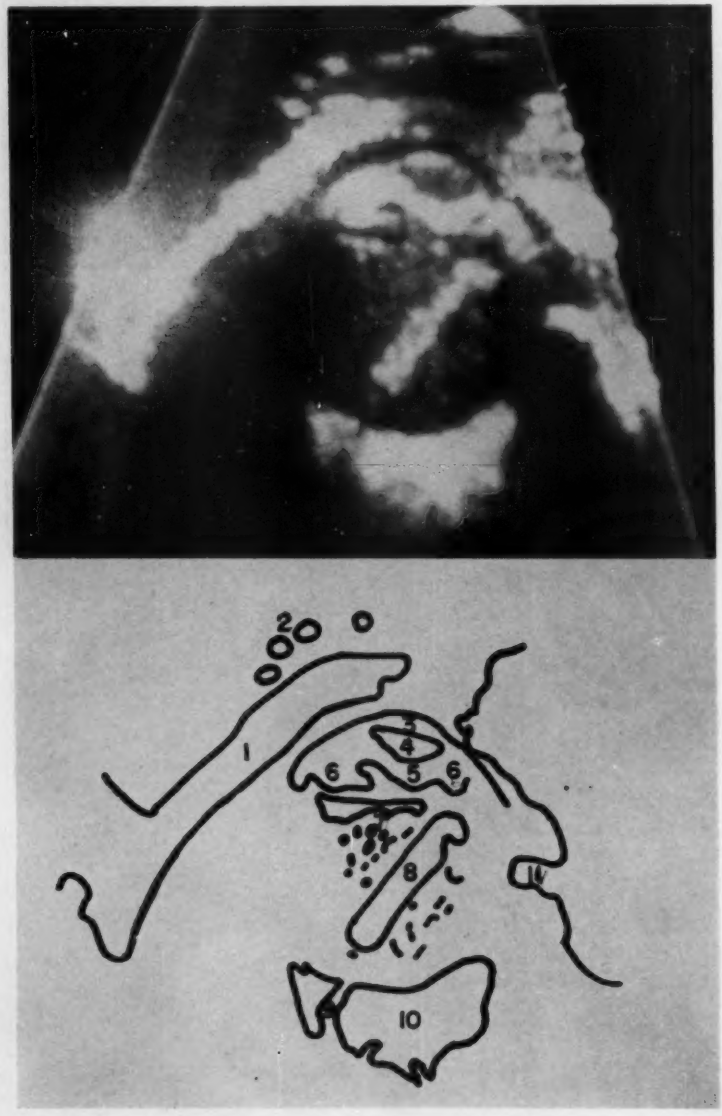
The commonest use for the sonic slit lamp is the visualization of the light-opaque eye, e. g., in cases of opacification due to corneal opacification, cataract, or vitreous hemorrhage or exudate. The following cases will demonstrate the diagnostic poten-

tials of this instrument. At present no other device can divulge the information obtainable with this device.

Differential Diagnosis in Complicated Retinal Detachments.—Diagnosis in retinal detachment is frequently complicated by semiopaque or totally opaque refractive media or by the presence of a tumor or radiolucent foreign body.

Figure 8 shows the eyes of a patient with corneal edema, hyphema, surgical aphakia, and a massive vitreous hemorrhage (no

Fig. 10.—This figure best demonstrates the lateral check ligament (*11*) and the passage of the optic nerve (*9*) into the orbital fat. *1*, lid; *2*, cilia; *3*, cornea; *4*, anterior chamber; *5*, iris; *6*, ciliary body; *7*, vitreous bands and hemorrhage; *8*, detached retina; *9*, passage of optic nerve through sclera into the orbit; *10* orbital fat; *11*, check ligament of the lateral rectus muscle.

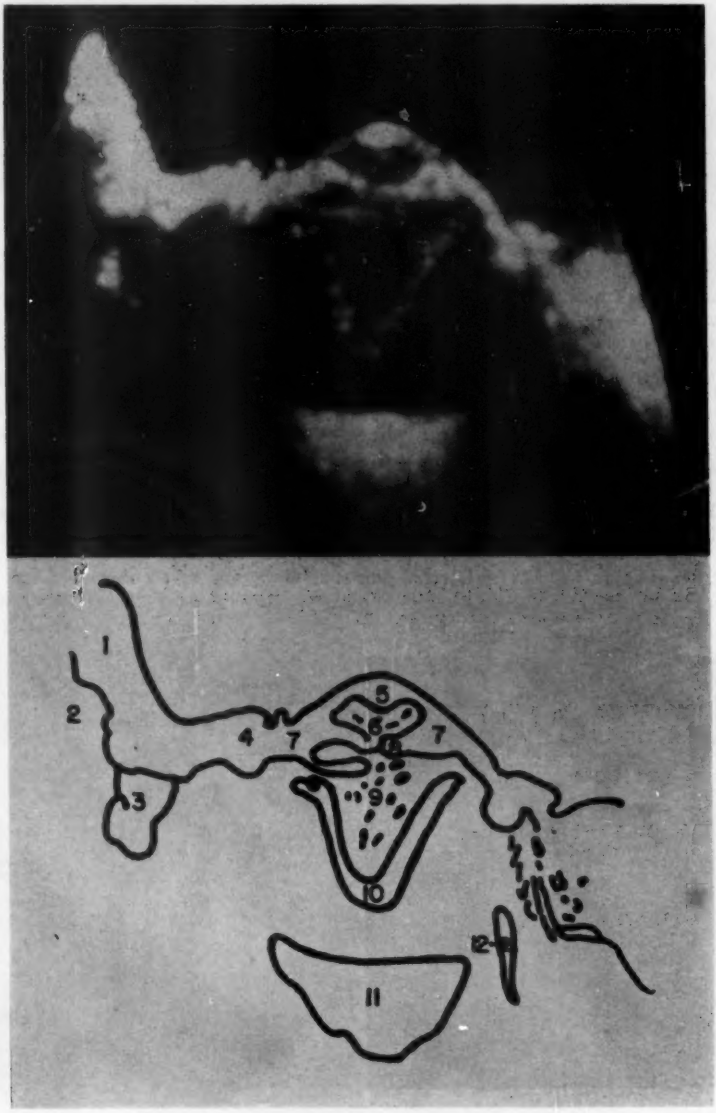


fundus reflex), which made it impossible to visualize the fundus.*

* Drs. A. Haft and M. Bernstein, of the Ophthalmology Service, Bronx Veterans' Administration Hospital, referred this patient and supplied the clinical data.

An ultrasonogram of the area (Fig. 9) prior to enucleation of the eye demonstrated the above findings. In addition, the sonogram demonstrated that the retina was wholly detached and that the vitreous hemorrhage was contained within the detached

Fig. 11.—The lateral rectus muscle is visualized at (*12*). *1*, nose; *2*, nasal cavity; *3*, nasolacrimal sac; *4*, caruncle; *5*, cornea; *6*, anterior chamber; *7*, ciliary body; *8*, iris; *9*, vitreous hemorrhage and bands; *10*, detached retina; *11*, orbital fat; *12*, lateral rectus muscle at level of the posterior pole of the eye.



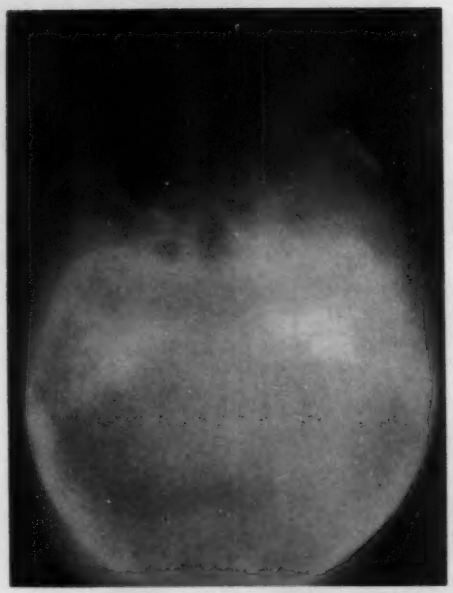


Fig. 12.—Transverse x-ray tomogram at the level of the superior and middle turbinates of the nasal cavity. Note the complete absence of any soft tissue detail within the orbits. (Drs. Bernard Roswit and Sol Ungar, of the radioisotope section, Bronx Veterans' Administration Hospital, furnished this tomogram, as well as its interpretation.)

retina. The subretinal fluid was relatively clear. This pathology was visualized despite the total opaqueness to light.

The nasolacrimal sac, the optic nerve and the orbital fat about it, and the check ligament of the lateral rectus muscle are well visualized in Figure 10. The intraorbital portion of the lateral rectus muscle in the area of the posterior pole of the eye is demonstrated in Figure 11. This interpretation is based on the normal anatomy of the area.

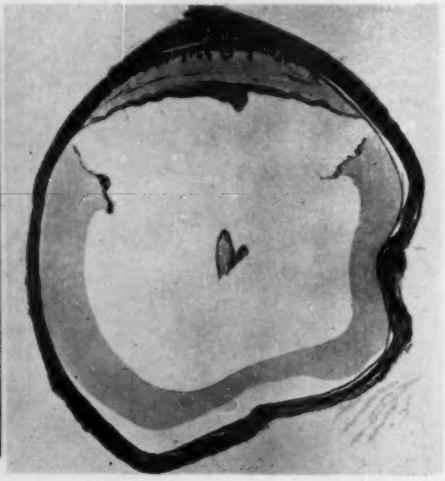
Figure 12 is an x-ray tomogram of the orbit. The greater clarity and definition of the soft tissues in the ultrasonic tomogram are evident upon simple comparison.

After enucleation, serial ultrasonic tomograms were made. These demonstrated total retinal detachment and the relative position of the retina at different levels within the eye. Serial tissue sections through approximately the same areas of the globe confirmed the ultrasonograms (Figs. 13 to 21).†

These sonic sections are made through the intact eye, just as slit-lamp sections are. The sonic tomograms were taken in steps of approximately 1.5 mm. from top to bottom at right angles to the anterior-

† By error, the pathological sections which more exactly correspond to the ultrasonograms were destroyed. However, the remaining sections confirm the ultrasonographic findings.

Fig. 13.—Figures 13 to 21 show serial ultrasonic tomograms of the enucleated eye of the patient in Figure 8. Note the change in the position of the retina at different levels through the eye.



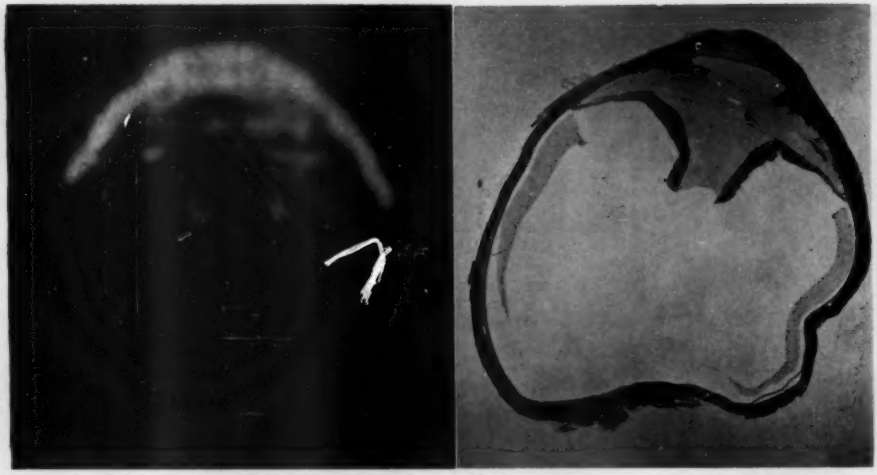


Figure 14

posterior axis, i. e., in both the sagittal and corneal planes.

Figure 16 implies that the vitreous bands may be visualized with the locator. The bands in this section were vascularized, which may account for their visualization. Further study of this point is necessary.

The sections in Figures 14 to 20 exhibited the following pathology: neovascularization and scarring of the cornea, hyphema, anterior synechiae which formed a false angle, entropion of the iris with connective tissue strands radiating to the ciliary body, hemorrhage about the ciliary body, vitreous bands and hemorrhages, total retinal detachment, and clear subretinal fluid. The sections in Figures 13 and 21 were cut above and below the cornea, and so none of the anterior chamber pathology appears in these sections.

Vitreous Hemorrhage.—The criteria which differentiates a simple vitreous hem-

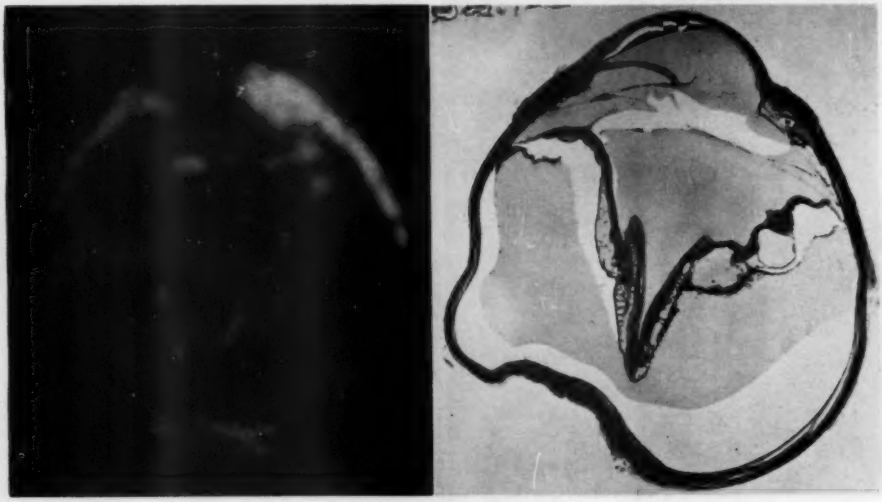


Figure 15

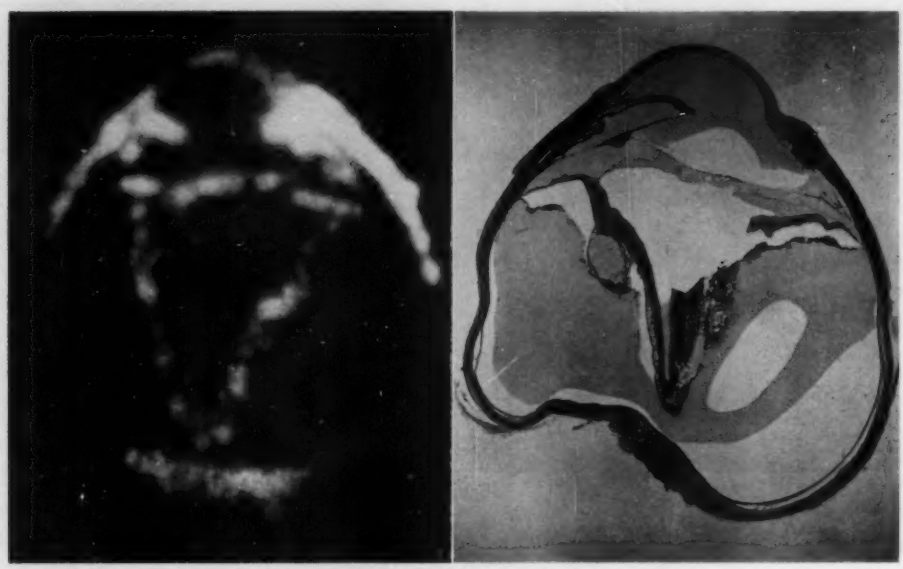


Figure 16

orrhage from vitreous hemorrhage with retinal detachment are the diffuseness and lack of structure of vitreous hemorrhage and the faintness of the echo. These points are well demonstrated in Figure 22.

This is an ultrasonogram of an aphakic patient who tore off his bandage and stuck his finger into his eye on the sixth postoperative day. A massive vitreal hemorrhage resulted, which totally obscured the fundus. The patient was referred for a determination of the extent of injury to his eye. On the basis of the ultrasonic findings of only a vitreous hemorrhage, a

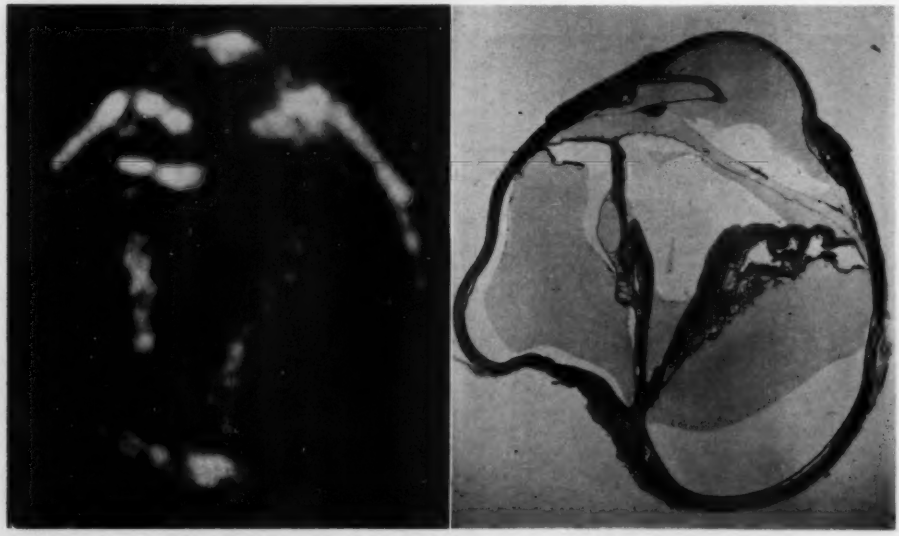


Figure 17

Figure 18

favorable prognosis was rendered. This was subsequently borne out as the vitreous cleared.

Tumors.—Another major problem in diagnosis of retinal detachment is the exclusion of a tumor as the primary etiological agent.

Figure 23 shows an eye that was enucleated because of a melanoma of the ciliary body, secondary glaucoma, and cataract. A tumor of the ciliary body was diagnosed because of scleral pigmentation near the tumor site, a pigmented mass visible gonioscopically in the angle and by transillumination.

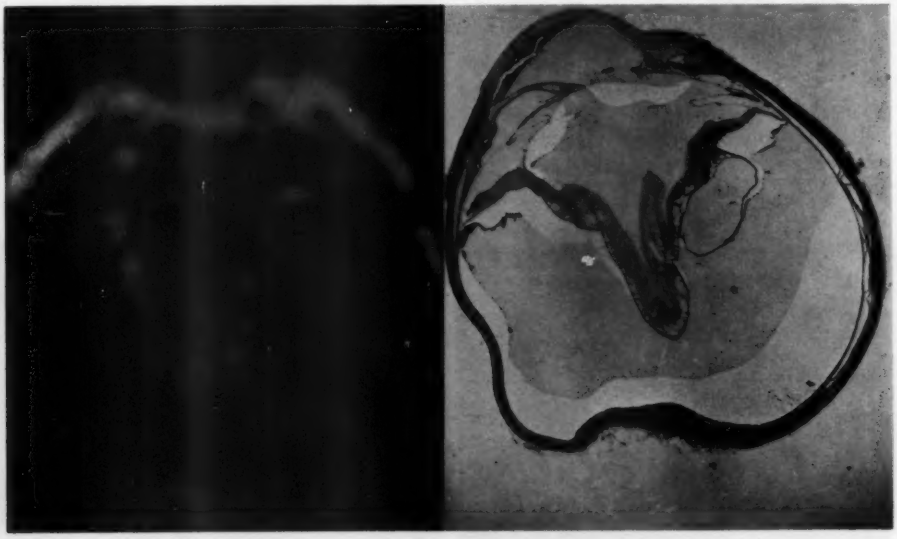


Figure 19

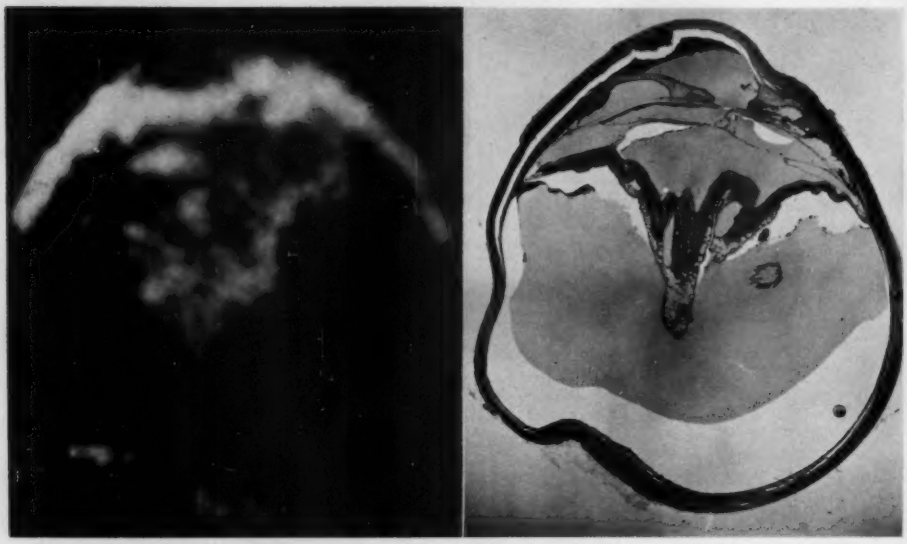


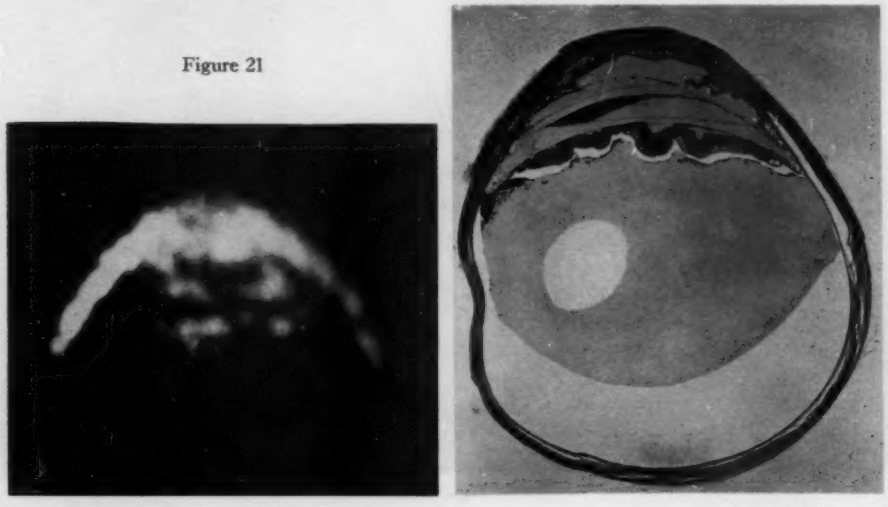
Figure 20

The diagnosis could be made in this instance without the ultrasonic locator because of the anterior location of the tumor. Had the tumor been more posteriorly located, it could not have been diagnosed with certainty prior to the removal of the cataract, as direct light visualization of the tumor would have been impossible. Radioisotope studies would have added little, as the Geiger counter cannot be placed over lesions near the posterior pole.

Despite the translucency to light caused by the cataract, there is no interference with sonic visualization of the anterior portion of the eye and even of the posterior pole.

Figures 24 to 31 are serial ultrasonograms of this eye. When these figures of the eye containing the tumor are compared with an ultrasonogram of a normal human eye (Fig. 32), one may see that the tumor

Figure 21



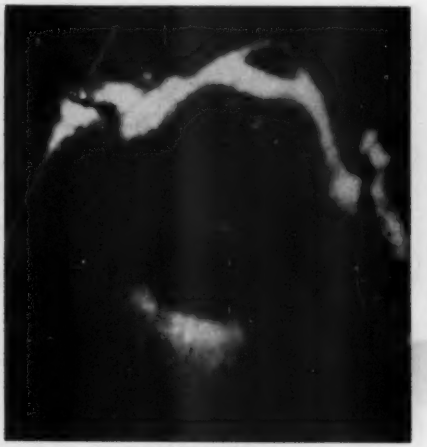


Figure 22

Fig. 22.—Ultrasonogram of an aphakic eye with a massive vitreous hemorrhage. Note the faintness of the echo as well as its random distribution.

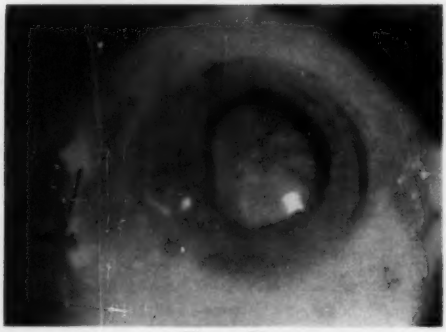


Figure 23

Fig. 23.—Gross appearance of eye containing a melanoma of the ciliary body. (Patient of Dr. Algernon B. Reese.)

Figure 24

Fig. 24.—Figures 24 to 31 show serial ultrasonic tomograms through an eye containing a melanoma of the ciliary body, shown in Figure 23. The posterior pole of the eye is visualized in Figures 29, 30, and 31 despite the dense cataract.

Figure 25

echo from the ciliary body tumor is absent in the latter.

Figure 24 is taken above the level of the tumor; Figure 31, below. The sonic tomograms are again in a coronal-sagittal plane. The remainder of the eye is clear of the tumor. This interpretation was confirmed by the histopathological section (Fig. 33).

Despite the cataract, the posterior portion of the eye is visualized. Sections of

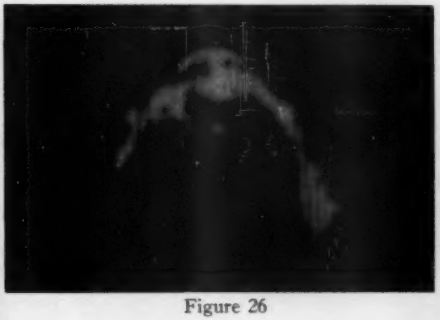


Figure 26

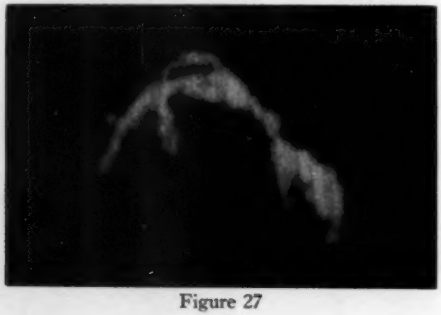


Figure 27

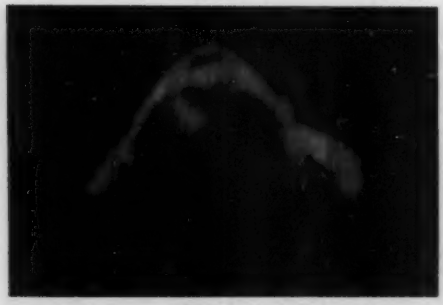


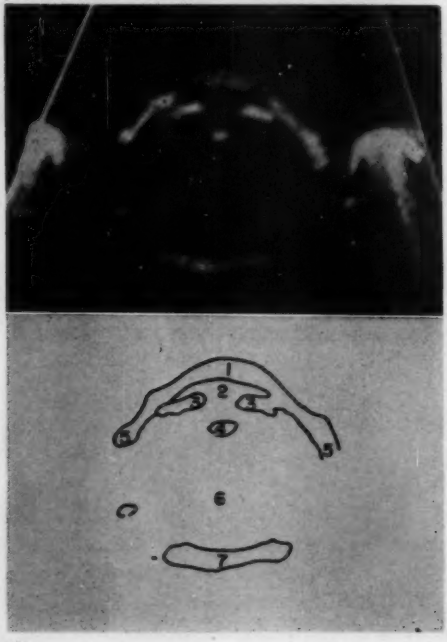
Figure 28

Figure 29

Figure 30

Figure 31

Fig. 32.—First known ultrasonogram of a human eye at 15 mc. *1*, cornea; *2*, anterior chamber; *3*, iris; *4*, lens; *5*, anterior sclera; *6*, vitreous; *7*, posterior sclera.



the sclera cannot be visualized with the present equipment without rotating the eye on its vertical axis. A new unit under construction will eliminate this and other defects. All of the eye can be visualized with the present equipment by having the patient rotate his eye. Thus, intraocular tumors at all depths may be visualized if they are larger than 1 mm. in size. This is independent of their response to radioisotopes.

Ultrasonographic interpretation of tumors is limited for the present to the recognition of an echo from an abnormal site.

All the factors which determine the strength of the echo have been determined and will be reported. Since the many variables can now be controlled, and corrected, a study has been initiated which will decide whether there is a difference between the type of echo from malignant and from benign tumors. The echos from foreign bodies are so much stronger than tissue echos that these can easily be distinguished.

Intraocular Foreign Bodies.—The next figure (Fig. 34) demonstrates this point.

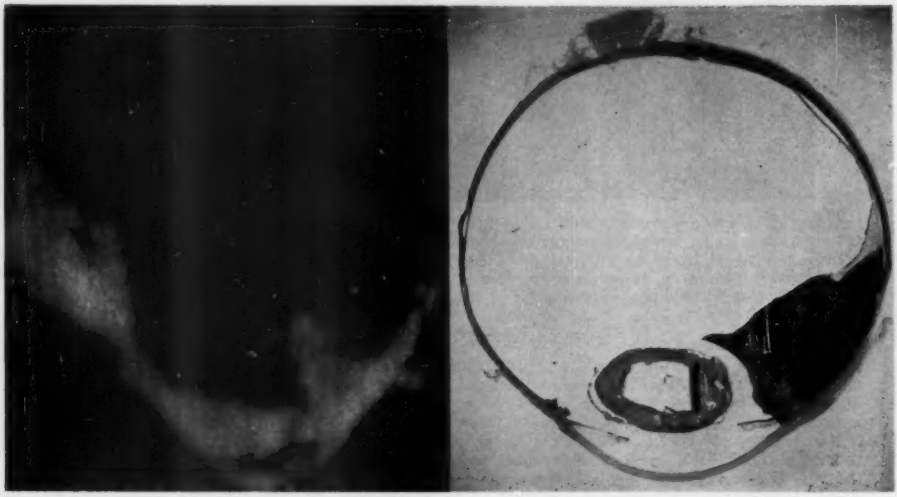
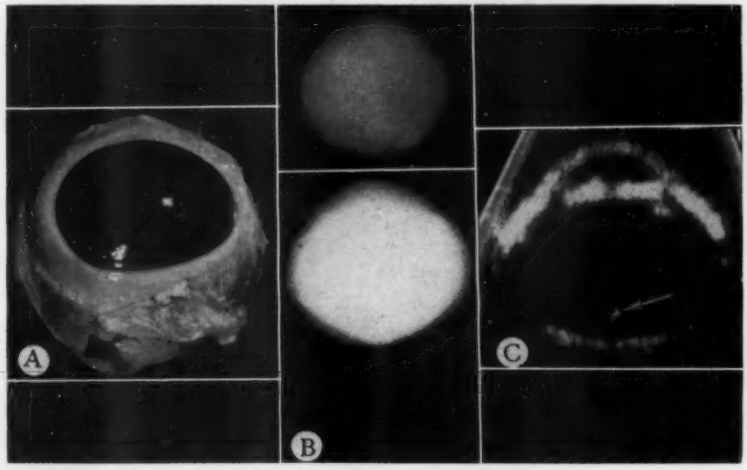


Fig. 33.—Histopathological section of eye in Figure 23, and an ultrasonogram through approximately the same area.

A piece of wood has been inserted into the vitreous of the eye. Although the wood cannot be distinguished on the x-ray, it stands out on the ultrasonogram.

Penetrating foreign bodies frequently will cause hemorrhage as well as retinal detachment. To determine if such a foreign body could be visualized in the presence of a vitreous hemorrhage, blood was injected into the vitreous of this eye (Fig. 35*A*). At maximum sensitivity the foreign body is obscured by the intravitreal blood. However, when the sensitivity of the system is reduced the echos from blood and tissue are, by comparison, so weak that they disappear and only the echo from the wood remains visible (Fig. 35*C*). Thus, radiolucent intraocular foreign bodies may be

Fig. 34.—Comparison of the gross (*A*), x-ray (*B*), and ultrasonic (*C*) appearance of an eye containing a piece of wood in the vitreous. The arrow on the ultrasonogram points to the sonic image of the wood. It is invisible to the x-ray. The precise position of the foreign body as to depth and azimuth may be found directly by the ultrasonic locator.



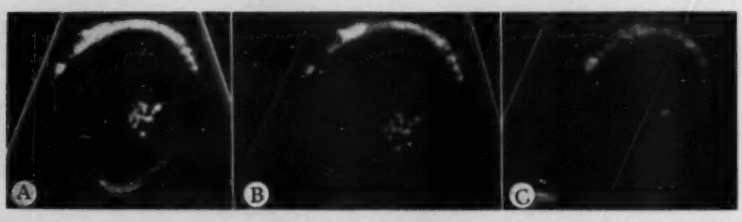
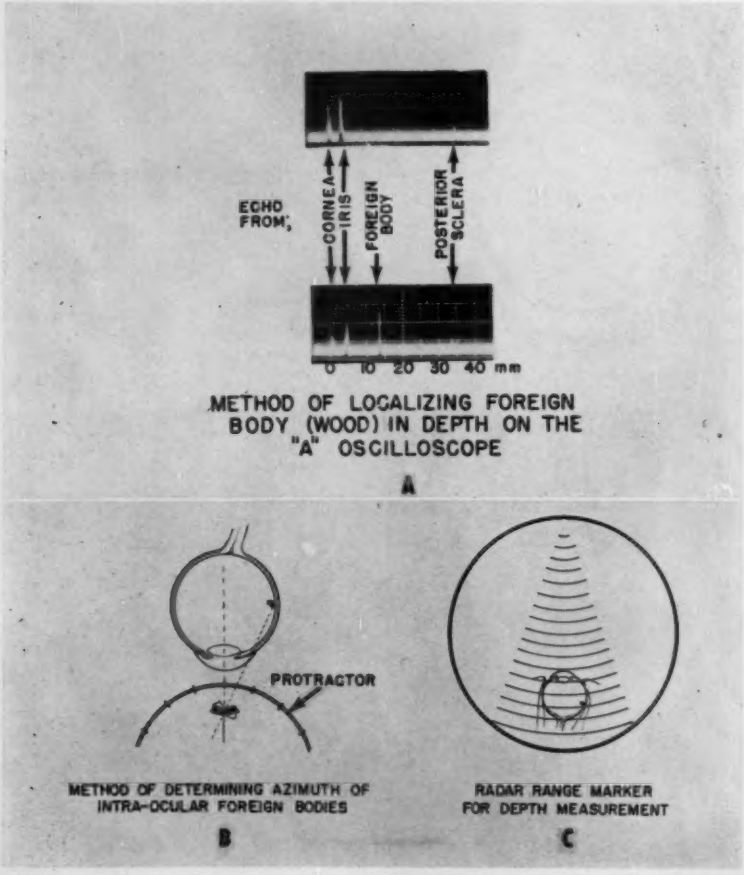


Fig. 35.—The appearance of blood and wood in the vitreous (the eye is viewed laterally through sclera). *A*, viewed with the full-strength transmitted sound beam. *B*, partially attenuated transmitted sound beam. *C*, attenuation of transmitted beam is increased to point at which the echoes from blood and the posterior surface of the eye disappear but the wood remains visible, thus permitting localization of the wood in the presence of blood in the vitreous.

Fig. 36.—Methods of visualizing and locating radiolucent intraocular foreign bodies with use of the combined radar and amplitude-modulated oscilloscope. *A*, measurement of the distance in relation to the major structure of the eye on the A, or amplitude-modulated, scope. Note that a strong foreign-body echo is interposed between the iris and rear-surface echoes. The change in the position of the rear-surface echo is due to the placement of the foreign body in a shorter portion of the eyeball. *B*, azimuth or angular position is determined by measuring the angular displacement of the transducer on a protractor. *C*, appearance on the radar scope when range markers are inserted. Depth can also be measured by calibrating the range markers.



localized, even in the presence of an opaque refractive media and hemorrhage.

Differential Diagnosis Between Vitreous Exudate and Hemorrhage and Between Retinal Detachment, Tumor, and Foreign Body.—Vitreous exudates lack a definitive outline. They are represented by a weak, diffuse, migrating echo (Fig. 22).

Retinal detachments may show similar characteristics, because of associated vitreous opacities, but at some point a strong definitive tissue echo will be located. The strong echo tends to be transient and to shift with the undulation of the retinal folds.

Tumors yield constant strong tissue echos which may be traced by serial tomography to the site of origin or base of the tumor.

The echos from foreign bodies are so strong that they remain after all the tissue echos have been eliminated by attenuation.

Foreign-Body Localization.—The exact depth and azimuth of a foreign body may be determined without any markers on the surface of the eye or in the tissue depth. This is accomplished by calibrating in advance the distances along the trace line (Fig. 36*A*) or by electronically inserting marker points which have also been calibrated. The azimuth is determined by stopping the scanning head when the foreign body is seen and noting the angular direction of the transducer to the foreign body on a protractor scale (Fig. 36*C*).

Summary

The use of pulsed ultrasonic reflection techniques permits direct highly resolved visualization of soft tissues and radiolucent materials, without the use of contrast media. Foreign bodies may be localized without markers in the presence of opaque media. Tumors may be visualized regardless of their position or their selective response to radioisotopes. Criteria for the differential diagnosis of intraocular tumors, retinal detachment, and vitreous hemorrhages, despite the presence of light-opaque media, have been formulated.

Exposure to ultrasonic energy at the levels used in this device is completely safe. The ultrasonograms included in this paper are the equivalents of the first x-rays and should be evaluated in that light. Improvements in equipment will yield far-superior films, and experience, far-wiser interpretations.

Mr. Carl Klammer, of the Special Devices Center, Office of Naval Research, helped during the initial assembly of the equipment. The Department of the Navy and Air Force lent electronic equipment. Dr. Douglas H. Howry and Mr. Jerry Posekany, of Automation Industries, Boulder, Colo., assisted in the design of the transducers.

333 King. St.

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Retinitis Pigmentosa, External Ophthalmoplegia, and Complete Heart Block

Unusual Syndrome with Histologic Study in One of Two Cases

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Pigmentary degeneration of the retina (retinitis pigmentosa) may appear as an isolated finding unassociated with other systemic abnormalities. Often, however, the patient may present other abnormalities, a number of which occur frequently enough in association with retinitis pigmentosa to be recognized as a syndrome. The Lawrence-Moon-Biedl syndrome, consisting of pigmentary degeneration of the retina, obesity, mental retardation, hypogenitalism, and polydactyly, is such an example. There also may be other less common abnormalities, such as deafness, convulsions, ophthalmoplegia, cerebellar ataxia, and progeria (premature aging) associated with retinitis pigmentosa.

External ophthalmoplegia is one of the uncommoner abnormalities found associated with pigmentary degeneration of the retina. Barnard and Scholz [1] reported four cases of this association and concluded that the association was more than just coincidental. Walsh [2] agreed with them and stated that the association is not just fortuitous but rather represents a syndrome. He listed five cases that he had observed, one of which was reported by Barnard and Scholz. Chamlin and Billet [3] reported three cases of ophthalmoplegia and pigmentary degeneration of the retina. Cogan [4] mentioned this association in the recent edition of his book. Alfano and Berger [5] have recently reported a case of retinitis pigmentosa, ophthalmoplegia, and spastic quadriplegia. Erdbrink [6] even more recently reported a case of ocular myopathy associated with retinitis pigmentosa. None of these 13 patients whose cases have been reported in the literature were said to have had heart block associated with the ophthalmoplegia and pigmentary degeneration of the retina. Kiloh and Nevin,[7] in their discussion of external ophthalmoplegia, listed approximately 100 reported cases of chronic progressive ophthalmoplegia, from the first one of von Graefe in 1868 through those reported in 1948, and there is no reference to either retinitis pigmentosa or atrioventricular heart block. Sandifer [8] reported a typical case of external ophthalmoplegia in which bundle-branch block was present, but the patient was not known to have retinitis pigmentosa.

Recently we have seen two patients with pigmentary degeneration of the retina, external ophthalmoplegia, and complete heart block. The apparent rarity of such a triad and the fact that necropsy following death of one of these patients provided us an opportunity for histologic study prompted this report. In spite of the rarity of the finding in these two patients, it is difficult to believe that the association is merely coincidental.

Report of Cases

CASE 1.—A 34-year-old Negro was first seen at the Mayo Clinic in 1948. His main complaint was loss of strength and shortness of breath on exertion. He stated that he had always been in good health until a few

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months prior to his visit. He was rejected by the army in 1941 because of a "spot" on his lung, although his physician in his home locality did not consider the lesion significant. He had gradually lost about 35 lb. over the previous five to seven years.

He was a slightly built man, weighing 128 lb. His radial pulse rate was 36 beats per minute. An electrocardiogram revealed an auricular rate of 52 and a ventricular rate of 32, there being complete atrioventricular dissociation. Although he did not have any visual complaints, bilateral ptosis and external ophthalmoplegia were noted. He stated that these had developed when he was about 20 years old. The ptosis was graded by the neurologist as +2 (on the basis of +1 to +4) bilaterally, and the limitation of ocular rotations, as −3 or −4 (on the basis of −1 to −4) in all directions except downward. The latter seemed to be normal. No note was made at this time regarding the appearance of the fundi. It was felt that the hilar shadow seen on the roentgenogram of the chest represented a hamartoma. The remainder of his examination showed normal conditions.

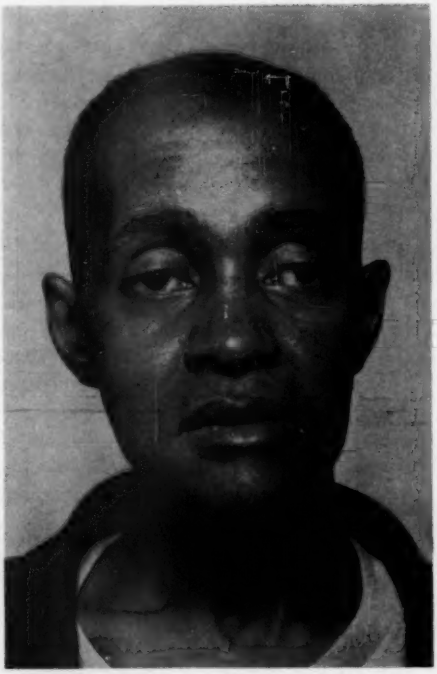

Fig. 1 (Case 1).—Patient with retinitis pigmentosa, external ophthalmoplegia, and atrioventricular heart block.

His next visit to the clinic was in December, 1956, because of increasing symptoms of cardiac decompensation. He was hospitalized for treatment of the mild congestive failure. Physical findings were similar to those of the previous visit, including the atrioventricular heart block and the abnormal shadow in the roentgenogram of the chest.

Ophthalmologic examination was requested because of the ptosis, divergent strabismus, and abnormal ocular movements (Fig. 1). The vision was good in each eye, 14/21 size print being read with ease. The pupils were normal in all respects. Bilateral ptosis, Grade +2, of each upper lid and almost complete external ophthalmoplegia of each eye were present. Ophthalmoscopic examination showed optic discs of good color, and the retinal vessels appeared normal. The pigment epithelium of the retina had a peculiar stippled appearance and a metallic sheen which was particularly marked around each optic disc. The choroidal vessels were prominent and were seen clearly in the areas around the nerve heads. No actual pigment clumping could be found, even in the more peripheral portions of the retinas. Visual fields were plotted and showed a huge enlargement of the normal blind spots, which seemed to match the areas of most markedly disturbed retina around the discs. The history of night blindness was not good, but the patient did admit on questioning that he had more trouble seeing in the dark than his wife did and that she always had to unlock the front door for him at night since he never did seem able to find the lock.

Neurologic examination disclosed generalized depression of the muscle stretch reflexes and slight weakness of the facial musculature. This latter finding is not uncommon in patients with chronic progressive

external ophthalmoplegia. Electromyographic studies were carried out on the triceps, deltoid, biceps, frontalis, and orbicularis oculi muscles; no evidence of a defect in neuromuscular conduction was demonstrated. No electromyographic studies were done on the extraocular muscles.

This patient had chronic progressive ophthalmoplegia, atrioventricular heart block, and a type of pigmentary retinal degeneration. The latter was atypical in that it was mainly confined to the area surrounding each optic disc and the field defects were not those typical of retinitis pigmentosa. Pigmentary degeneration in a Negro is said to be rare, and it is interesting to point out that one of the patients described by Walsh [2] with ophthalmoplegia and pigmentary degeneration of the retina was also a Negro.

CASE 2.—A 17-year-old white boy came to the clinic in September, 1955, because of spells of unconsciousness. He was said to have been a normal child until the age of 3 years, when the parents noticed that his eyelids began to droop. Shortly thereafter his eyes were noted to be divergent. At this time he was smaller than other children of his age and he did not seem to be growing. He had weighed 35 lb. at 1 year of age, and he remained at this same approximate weight until he was 5 years old. A progressive deafness began at about the age of 4 years, and he began experiencing difficulty going down the stairs because he seemed unsure of his footing. His parents thought that he had always been less active physically than other children, and he did not like running or jumping. He had reached the level of a junior in high school but had had to repeat the fourth grade because of poor work.

Two months prior to admission to the clinic the boy began to have spells of unconsciousness about once every 2 to 10 days, but they had occurred as often as three times in a single day. The attacks consisted of a period of deep breathing, at which time he described a hazy vision of 10 to 15 seconds followed by a period of unconsciousness. He often fell and remained unconscious for a few seconds to 15 minutes. These attacks had become so frequent that the patient was afraid to stand alone and preferred to hold onto his father's hand while walking.

On examination body proportion was normal but he was small for his age. There was no beard, and pubic and axillary hair was scanty. The genitalia were small but otherwise normal. The radial pulse rate was 42/min. There was marked bilateral loss of hearing, but accurate study of this was not completed. Results of laboratory examinations, including roentgenograms of the skull and chest, were negative. The electrocardiogram showed complete atrioventricular dissociation, with an auricular rate of 95 and a ventricular rate of 37.

The central vision was normal in each eye (14/21 print on the A. M. A. reading card). The patient compensated for marked ptosis of each upper eyelid by holding his head back. The eyes were divergent approximately 15 degrees, and little if any ocular rotation could be elicited. The pupils reacted promptly to light and in accommodation. Ophthalmoscopic examination showed discs of fairly good color, but the arterioles were attenuated. The pigmented epithelium was mottled and had a fluorescent appearance. This change was most marked around each optic disc but did extend to some extent to the periphery, where there was some clumping of pigment of the type seen in more typical retinitis pigmentosa. The visual fields were plotted with both perimeter and tangent screen and showed the characteristic defects of retinitis pigmentosa (Fig. 2).

Cardiac consultation was obtained, and it was the impression of the cardiologist that the episodes of syncope were on the basis of an asystole, although at no time was an electrocardiogram obtained during an attack.

Three days after admission a severe episode occurred, necessitating intravenous administration of epinephrine and artificial respiration. Cyanosis, cardiac arrest, and

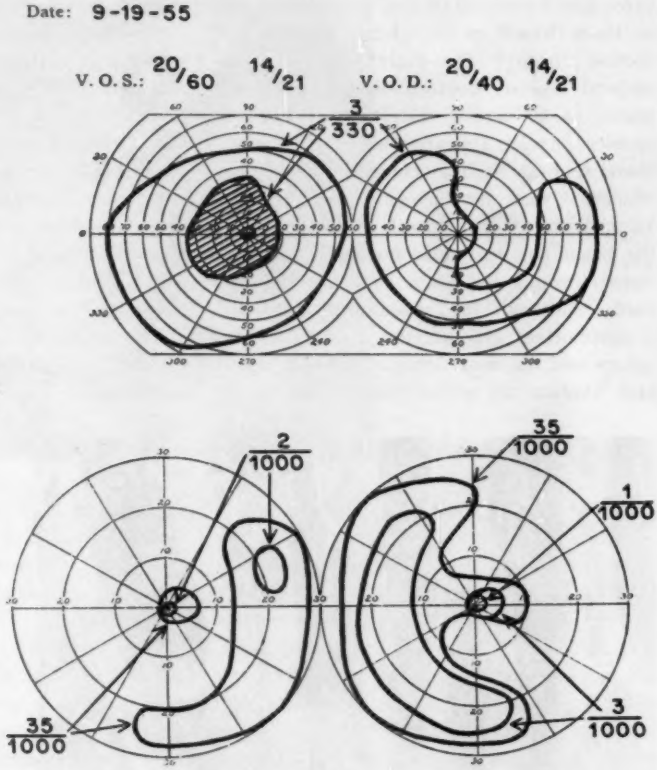

Fig. 2 (Case 2).—Visual fields as plotted with the perimeter and tangent screen.

Cheyne-Stokes respiration were observed during the attack. Complete recovery from this attack occurred, but the next morning a similar attack occurred which led to the patient's death.

Necropsy Findings.—The body was small for the stated age. There were genital hypoplasia and mild gynecomastia. The heart appeared normal. The lungs were edematous. The thyroid and testes were small. The brain, spinal cord, and muscles appeared normal. The posterior segment of the left globe along with several extraocular muscles was removed.

Routine histologic examination of the heart failed to reveal any abnormality in the conduction system or muscles. The gross diagnosis of the lungs was confirmed by the finding of edema fluid with a few red cells in the alveoli. The testes showed immaturity of tubular development, and the thyroid, though small, did not appear abnormal. The remainder of the thoracoabdominal organs were essentially normal. Histologic examination of the brain demonstrated marked siderosis of the globus pallidus, the iron being not only in the blood vessels but in granules scattered diffusely throughout the walls of small capillaries. Occasional swollen astrocytes and, in addition, some microglial cells containing golden-brown pigment were present in this location.

In the brain stem the neurons of the third, fourth, and sixth nerve nuclei and their fibers appeared normal. There was a loss of neurons in the lateral portions of the substantia nigra, with an increase in astro-

cytes and deposition of iron granules similar to those found in the globus pallidus. A section through the eighth nerve nuclei showed loss of neurons in the vestibular nuclei with similar siderosis, while the cochlear nuclei appeared intact. An additional finding, the importance of which was obscure, was the presence of marked vacuolation of the central white matter of the brain and lenticular nuclei, which persisted through the brain stem and cervical cord. Although the appearance suggested a postmortem artifact, the location of the spaces and the short interval between death and fixation by embalming of the brain suggest that some other factor was present.

Histologic examination of the extraocular muscles showed diffuse loss of muscle fibers and an increase in loose connective tissue and fat. The fibers varied considerably in size. The scattered remaining normal fibers were intermixed with degenerating fibers. These latter were sometimes swollen and sometimes atrophic. A typical degenerating fiber would consist of a portion staining normally with a gradual swelling and separation of the fibrils, then a loss of cross striations in the individual fibrils, leaving a greater or less amount of granular material within the sarcolemma (Fig. 3*a* and *b*). The nuclear

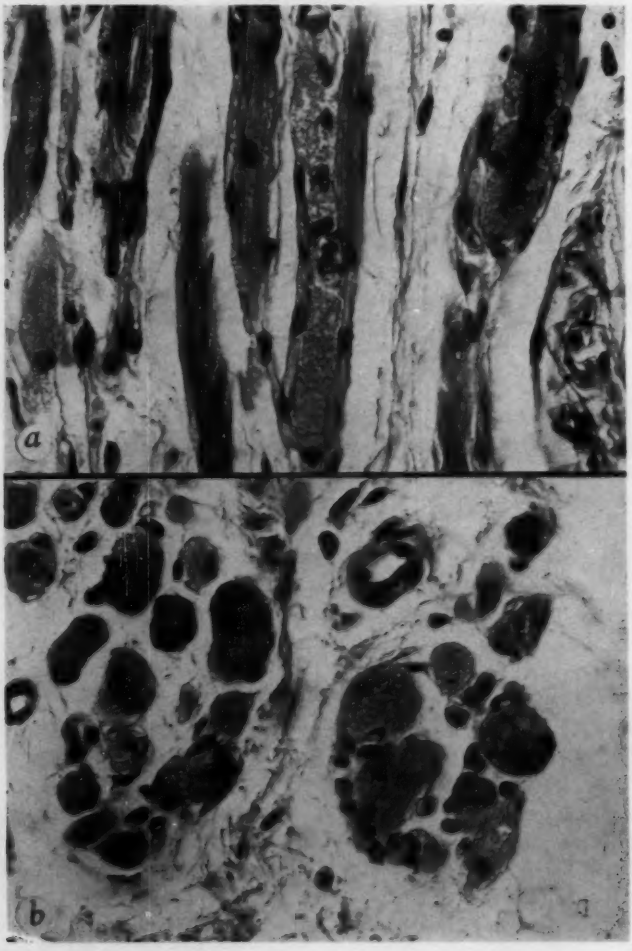

Fig. 3.—Extraocular muscle. Normal fibers intermixed with fibers undergoing granular degeneration. (*a*) Longitudinal section; hematoxylin and eosin; ×460. (*b*) Cross section; hematoxylin and eosin; ×500.

Fig. 4.—Extraocular muscle. Normal and degenerating muscle fibers with intact motor nerve. Bodian stain for axis cylinders; × 175.

changes were not marked, though some nuclei were rounded with prominent nucleoli. In a few areas there were clumps of distorted nuclei in the degenerating muscle cells; such clumps, however, were relatively uncommon. No evidence of basophilia of the sarcoplasm or fibrillar regeneration was found. In only a few areas was the number of nonmuscle nuclei increased. Careful observation of the interfascicular nerves after either routine or special neurologic staining showed no evidence of degeneration (Fig. 4). The findings were typical of a primary myopathy.

The numerous sections of the posterior segment of the globe, cross sections of the optic nerve, and mounted flat retinal preparations were studied extensively. Grossly, the posterior segment looked fairly normal. After the central portion of the globe was prepared in the usual manner for paraffin histologic sections, it was found that the remaining portions of the retina could be stripped from the underlying choroid with only a little, if any, more resistance than a normal posterior segment of retina gives. On transillumination the retina appeared to have numerous atrophic areas. These areas

Fig. 5 (Case 2).—Retina of patient with retinitis pigmentosa, external ophthalmoplegia, and atrioventricular heart block, showing an area of typical retinitis pigmentosa to the right. Note the normal layer of bipolar cells and the absence of the outer nuclear layer and rod and cone layer. Hematoxylin and eosin; × 125.

were round lesions scattered over the retina in an irregular manner. No pigment was visible in the retina on gross examination, and there was no evidence that the pigmented epithelium was adherent to any of the retina removed.

Histologic cross sections of the posterior segment showed areas of fairly normal-looking retina intermixed with areas of greatly disturbed retinal architecture (Fig. 5). In the areas of disturbance the retina appeared to be adherent to the underlying choroid, while in the more normal areas of retina there was the usual postmortem separation. The choroid appeared normal except for the areas of retinal adherence. The usual amount of choroidal pigmentation was present, and no sclerosis of the choroidal vessels was detected. The pigment epithelium could be identified only in a few places; for the most part it was entirely absent. In the areas of retinal disturbance only the outer layers of the retina, the rods and cones and the outer nuclear layers, were affected. These outer layers were completely absent in some areas and at the point of junction with normal retinal elements were distorted by fibrosis. The bipolar-cell layer and the ganglion-cell layer were normal throughout the retina and passed over the aforementioned disturbance unaffected.

Bodian, Weil, and Weigert stains of the optic nerve in both longitudinal and cross sections showed the axis cylinders and their myelin sheaths to be normal. This indicated absence of optic atrophy (Fig. 6*a* and *b*).

Portions of the retina not used for paraffin section were placed flat on glass slides and stained with a variety of stains and mounted in glycerine without compression by the cover slip. In these specimens pigment clumping along the walls of the smaller retinal vessels could be seen (Fig. 7*a*). Examination of these flat specimens

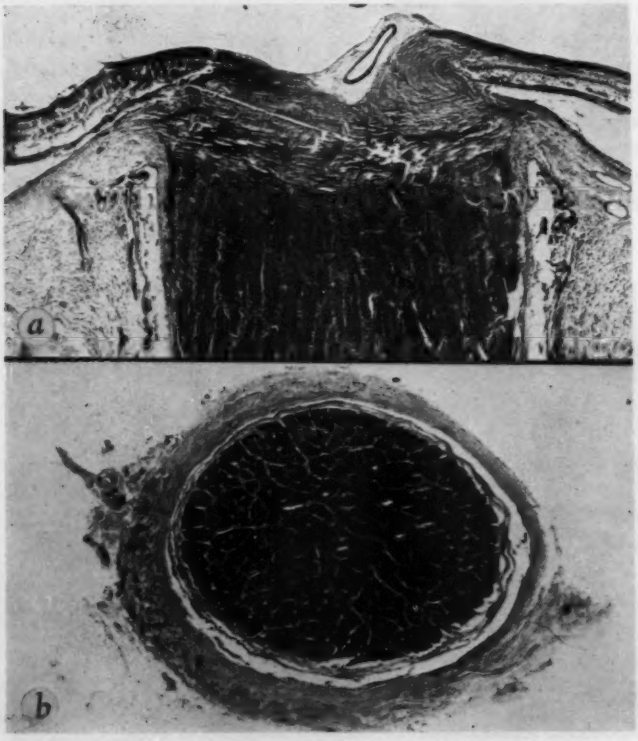

Fig. 6 (Case 2).—(*a*) Longitudinal section through optic disc and nerve, demonstrating absence of optic atrophy in patient with retinitis pigmentosa. Weigert stain; ×27. (*b*) Cross section of same optic nerve. This nerve is perfectly normal, with no evidence of atrophy. Weigert stain; ×17.

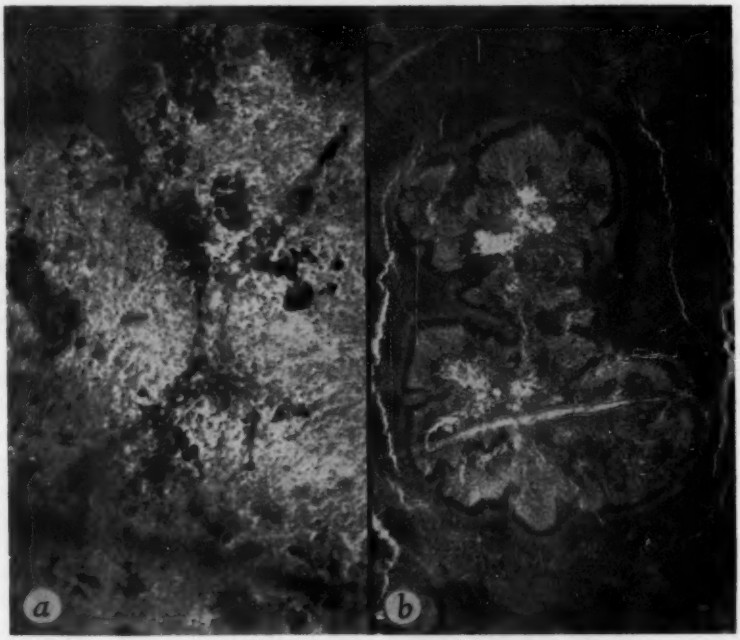

Fig. 7 (Case 2).—(*a*) Mounted flat retinal preparation, showing deposition of pigment along the smaller retinal vessels. Periodic acid-Schiff stain; × 140. (*b*) Giant pseudorosettes seen in the mounted flat retinal preparation of patient with retinitis pigmentosa. Giemsa stain; × 25.

revealed a bizarre abnormality that we had not encountered before. This consisted of circinate atrophic areas that seemend to be the horizontal counterpart of the retinal atrophy seen grossly and the areas of disturbed neuroretina elements seen on histologic examination of cross sections of the retina. One of these lesions is shown in Figure 7*b*, and, as can be seen, the pattern is that of a giant "pseudorosette." The center of the lesion is thinner than the surrounding normal retina, and the border of the lesion is surrounded by a palisade of cells. This border of cells appears to be the normal cells of one of the nuclear layers of the retina, probably the outer nuclear layer, that seem to have changed their polarity and are running in a more horizontal plane. It appears that these cells are being drawn by fibrosis toward the center of the lesion, where this layer of cells is completely absent.

Comment

The two patients reported here are examples of the unusual association of pigmentary degeneration of the retina, external ophthalmoplegia, and atrioventricular heart block.* The association of this triad of

* Dr. Richard C. Horns, of Minneapolis, gave us the opportunity of examining a patient who seemed to have a condition related to the one under discussion. Her only complaints were those due to a peculiar keratitis, but in the course of examination she was found to have a pigmentary degeneration of the retina. It was thought that the retinal changes were probably inflammatory or toxic rather than those of true retinitis pigmentosa. She had previously used considerable amounts of quinine in treatment of malaria contracted in missionary work abroad. This patient died unexpectedly shortly after her clinic visit, and Dr. Horns informed us that at necropsy the retina showed the typical findings of retinitis pigmentosa and that her death was attributed to heart block. She did not have external ophthalmoplegia.

findings has not been reported previously to our knowledge. In our second case, in which necropsy material was available for study, we had the unusual opportunity of studying two conditions in which histologic material is scarce, namely, chronic progressive external ophthalmoplegia and retinitis pigmentosa.

According to Cogan,[9] only about 20 pathologic descriptions of retinitis pigmentosa are recorded in the literature and only 9 of these could be considered authenticated by the clinical and histologic findings. He added three more previously unreported cases, which brought the total number to 12. Lucas [10] has recently reported the pathologic findings in two additional cases.

Cogan listed the factors which in his opinion enable one to make the pathologic diagnosis of retinitis pigmentosa: 1. A correct clinical diagnosis should have been made. 2. Changes should not have occurred through other disease to mask or confuse the process under study. 3. The typical histologic features of retinitis pigmentosa are (*a*) absence of the rod and cone layer, (*b*) absence of most of the outer nuclear layer, (*c*) accumulation of melanin granules in the retina, (*d*) varying amounts of gliosis, (*e*) little if any abnormality of bioplar cells and ganglion cells, and (*f*) no optic atrophy.

The histologic changes in the retina and the absence of optic atrophy in our second patient fulfilled Cogan's postulates. In addition, we noted the atypical feature of patchy distribution of these changes which on the mounted flat retinal preparation appeared as giant pseudorosettes, a feature not previously reported.

Wolter [11] has recently described finding rosettes in the retina of a patient with retinitis pigmentosa. He described these rosettes as being composed of very undifferentiated cylindrical cells arranged horizontally in the retina. He thought that the appearance suggested that these rosettes represented reactive formations of pathologic astroglia. The lesions in the retina of our patient were much larger and entirely different in appearance from those reported by Wolter. The rosettes described by Wolter were composed of very undifferentiated cylindrical cells with long glia-fiber-like processes which were arranged horizontally in the retina in close relationship to the hyalinized choriocapillaris. The rosettes which we have described were considerably larger and irregular in shape and appeared to have no relationship to individual blood vessels, but they did appear to be related to the areas of atrophy of the retina. These giant pseudorosettes seemed also to correspond to the areas of disturbed retinal architecture seen on the routine paraffin cross sections.

Examination of the extraocular muscles and the motor nuclei supplying these muscles allowed us to determine that the primary lesion was in the muscle itself and that the nuclei and peripheral nerves were essentially normal. This finding of a peripheral myopathy rather than a central neuropathy is in accord with most recent authors, including Kiloh and Nevin,[7] who proposed that the term "ocular myopathy" be used for this condition. Thus the condition "chronic progressive nuclear ophthalmoplegia," as used by many of the earlier writers on this subject, is now more properly referred to as "chronic progressive ocular myopathy."

The etiology of the heart block, the third portion of the syndrome in our two patients, remains obscure. We also do not understand the significance of the degenerative changes in the globus pallidus and the substantia nigra. The peculiar degenerative changes in the vestibular portion of the eighth nerve nuclei may be related to the deafness, although no such changes could be demonstrated in the cochlear nuclei. The lack of sexual maturity has been frequently described with pigmentary degeneration of the retina. Perhaps the small size of the thyroid gland complements this picture.

Summary

Two cases of pigmentary degeneration of the retina, external ophthalmoplegia, and

complete heart block are reported. This triad of findings comprises an unusual and previously unreported syndrome.

Necropsy in the second case made possible histologic study of the retina and optic nerve, the extraocular muscles, and the nuclei of the brain stem. The retina showed typical changes of retinitis pigmentosa. In addition, bizarre giant pseudorosettes were demonstrated on mounted flat retinal preparations. Myopathic changes in the extraocular muscles and the lack of changes in the motor nuclei of the nerve supplying these muscles indicated that the opthalmoplegia in this patient was a chronic progressive ocular myopathy rather than a chronic progressive nuclear ophthalmoplegia.

Mayo Clinic.

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Application of Poiseuille's Law to Aqueous Outflow

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Since the perfusion rate of an enucleated eye is very near that of the perfusion rate in vivo,[1,2] it is reasonable to infer that nervous or "life" forces are not a constant influence on this in vivo rate and that the outflow is governed primarily by physical laws of flow. It is important, therefore, to ascertain the quantitative expression of the physical factors which govern the outflow rate. Poiseuille's law, ordinarily considered as dealing with viscosity of solutions, is actually an expression of the fundamental law governing laminar flow of liquids through cylindrical tubes.

The application of any physical law to biological processes must be done with great caution and with due respect to the limitation inherent both in the law itself and in biological systems. In general, investigators[3] are more inclined to apply this law to aqueous outflow than to blood flow because the aqueous is a noncellular low-protein-content liquid which should behave in a Newtonian fashion.

Goldmann[4] prepared a formal mathematical treatment of aqueous outflow according to Poiseuille's law. He treated the more general case of elliptical rather than circular tubes. At that time there were insufficient data for specific application of the formulae to the aqueous outflow. There now appear to be enough reliable data in the literature to attempt such an application. The simplified form of Poiseuille's law will be used rather than Goldmann's formulations. The simplified form applies to the special case of laminar flow through cylindrical tubes and may be expressed in the following form[5]:

$$\eta = \frac{h\rho g \pi r^4 t}{8Lv} \qquad (1)$$

Where

η=viscosity (poise)
h=head of liquid (cm.)
ρ=density of liquid (gm/cm.^{3})
g=acceleration of gravity (cm/second^2)
r=radius of orifice (cm.)
t=time (seconds)
L=length of orifice (cm.)
v=volume of flow (cm.^{3})

This formula applies to a single tube, but there are numerous "tubes" in the outflow apparatus of the eye. We assume that a number of such single tubes will approximate the exit channels of the eye.

$$Nr_i^4 = \frac{ND_i^4}{16} \qquad (2)$$

N=number of holes or pores
r_i=radius of individual hole
D_i=diameter of individual hole

By using Equation 2 and rearranging Equation 1 we have

$$\frac{v}{t} = 24.1 \frac{h\rho ND_i^4}{L\eta} \qquad (3)$$

This equation relates the flow (v/t) to the numerical constant 24.1 and to the various variables. All of these variables appear to be interrelated in a linear fashion except the diameter of the tubes, which appears as the fourth power. It is this exponent which accounts for many of the peculiarities of flow which will be discussed later.

We are now in a position to approximate several of these factors for the normal eye. The normal "head of pressure" in the eye is the difference between the intraocular pressure and the episcleral venous pressure. This has been determined by Goldmann[4] to be 5 mm. Hg and by Linner[6] to be 4 mm. Hg. We will use a value of 5 mm. Hg, equivalent to 6.8 cm. H_2O.

$$h\rho = 6.8 \text{ gm/cm.}^2 \qquad (4)$$

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The normal flow of aqueous has been determined by Goldmann [4] to be 1.9μl. (microliters)/minute. Grant [1] and Becker [2] give C values $\left(C=\frac{\text{(Flow, } \mu\text{l/minute)}}{(P_o-P_v\text{, mm. Hg)}}\right)$ of about 0.28. If we use the value of 5 mm. Hg for P_o-P_v given above, the value is 1.4μl/minute. I have arbitrarily used a value of 1.4μl/minute, or

$$\frac{v}{t}=\frac{0.0014}{60}=2.37\times10^{-5}\text{ ml/second} \quad (5)$$

The length of the tubes is arbitrarily taken as 20μ. This is a compromise among several pieces of datum. Ashton [7] believes that 120μ is the thickness of the trabeculae responsible for the pressure drop. Flocks [8] estimates his "pore tissue" to be 20μ in thickness. Electron micrographs of Garron et al.[9] suggest that the distance between the inner wall of Schlemm's canal and the open trabecular meshwork would be on the average smaller than this, probably about 10μ.

$$L=20\mu=0.002\text{ cm.} \quad (6)$$

The viscosity is probably very near to that of water and is probably the most accurately estimated factor. The viscosity of water at 37 C is 0.695 centipoise. The following value is used:

$$\eta=0.007\text{ poise} \quad (7)$$

We may now substitute the above values (Equations 4, 5, 6, and 7) in Equation 3 and obtain by rearrangement

$$ND_t^4=2\times10^{-12}\text{ cm.}^4 \quad (8)$$

This equation tells us several interesting things.

1. For $N=1$, that is, if all the outflow went out only one hole, the diameter of that hole need only be 12μ in diameter. It follows, therefore, that trabecular meshwork having interstices greater than 12μ does not contribute to outflow resistance. This would indicate that the uveal and corneoscleral openings described by Flocks are not a factor in the normal outflow resistance.

Grant's experiment [10] in which he swept away the trabeculae and found no drop in pressure would corroborate the view that the main site of resistance is close to or in the wall of Schlemm's canal. The trabecular meshwork which was torn away was not contributing to the resistance, and hence its removal did not change the resistance.

2. At the other extreme, if the holes were rather uniformly about 0.6μ in diameter, some 110,000 holes would be needed. For this to have meaning in relation to the human eye, it might be well to approximate the filtration area of the human eye. The filtration area may be considered an annular ring whose

$$\text{Area}=\pi DW \quad (9)$$

Where

D=diameter of the eye at the level of Schlemm's canal

W=width of ring

The width of this filtration ring may be estimated from the work of Theobald,[11] who showed that the widest radial diameter of Schlemm's canal was about 0.5 mm. and that the width of the anterior-posterior diameter averaged 0.05 mm. Stereomicroradiographs of Pattee, Garron, McEwen, and Feeney,[12] showed the canal to be from 0.2 to 0.4 mm. in diameter. It is interesting that the melanin lines in two cases of pigmentary glaucoma * were about 0.1 mm.

Estimation of the Diameter of Schlemm's Canal

Method	Diameter, Mm. Max.	Av.	Min.	Reference
Histologic	0.5	0.05		11
Microradiographic	0.4		0.2	12
Melanin glaucoma	0.15		0.08	
Blood in canal	0.08		0.03	

(0.15 and 0.08 mm., respectively). Measurements of the width of the red line from a normal eye with blood in the canal * yields a value for the diameter of from 0.03 to 0.08 mm. The Table summarizes these various results. For purposes of calculation we have used the value of 0.2 mm. for the diameter of the canal, which, when multiplied by $\pi/2$, will give the curved width of about 0.3 mm.

$$W=0.3\text{ mm.}=0.03\text{ cm.} \quad (9a)$$

* Stereogonioscopic photographs were provided by Dr. Robert Shaffer. Values were corrected for gonioscopic lens and photographic enlargement.

The diameter may be obtained from the data of Wilmer et al.[13] to be 11.5 mm.

$$L=11.5 \text{ mm.}=1.15 \text{ cm.} \quad (9b)$$

The filtration area of the eye then becomes

$$\text{Area}=3.14\times1.15\times0.03=0.11 \text{ cm.}^2=11 \text{ mm.}^2 \quad (9c)$$

This, then, means that if the 110,000 holes about 0.6μ in diameter were distributed uniformly over the filtration area there would be some 10,000 holes per each square millimeter.

3. If the size of a hole is considered somewhere between the two extremes given above and more in line with the reported results of previous investigators, we would probably be dealing with a distribution of sizes from about 1.2μ to 3μ. For purposes of illustration let us consider holes of 2μ in diameter. For this size, 1200 holes would be needed to take care of the flow, or a little more than 100 holes per square millimeter of filtration area, or about 1 hole in a square 0.1 mm. on a side (0.01 mm.^{2} in area). This can be visualized by drawing a square 10 cm. (about 4 in.) on a side and placing within this square one circle about 2 mm. in diameter (about 3/32 in.). It then becomes obvious that the hole area is small in comparison with the nonhole area. This probably accounts for the difficulty of finding these holes in histologic preparations. This low porosity also accounts for the slowness of filtration through the eye as compared with an equal area, thickness, and hole size of filter paper, which has high porosity.

We may now return to Equation 3, which relates the rate of flow to the pressure, number of holes and their diameter, length of the hole, and viscosity. It has been shown by several investigators that the pressure is directly proportional to rate of flow.

If rate of flow is divided by the pressure, we obtain the constant C, the facility of outflow.

$$\frac{v}{thp}=C=24.1\ \frac{ND_1^4}{L} \quad (10)$$

Substituting again the values from Equations 6, 7, and 8 above, we obtain a numerical value for C as follows.

$$C=3.44\times10^{-4} \text{ cm.}^3/\text{gm. second} \quad (11)$$

This is, of course, the same numerically as the usual value of C of 0.28 expressed in units of $\frac{\text{mm.}^3}{\text{minute mm. Hg}}$.

Equation 10 indicates that in cases of glaucoma in which C is depressed either the number of holes or their diameter has to decrease or the length of the holes or the viscosity has to increase. The length of the holes is probably not subjected to much increase, and this is probably not an appreciable factor in glaucoma.

The viscosity of the aqueous probably varies between very narrow limits. Even in conditions in which there is excess protein present the viscosity is little changed. Usually the condition of flare or excess protein is caused by an inflammatory condition which decreases the production of aqueous resulting in a relatively soft eye.

We are thus usually confronted with the only variables responsible for causing increased pressure in the eye: the number of holes and their diameter. It is apparent that, of these two variables, the increase in pressure is less "sensitive" to changes in the number of holes than to changes in their diameter. If half of the holes are obliterated, the facility of outflow will be decreased by one-half. The pressure would then have to double, but it is just the pressure drop, the P_e-P_v, which would double. Since it is normally 5 mm. Hg, doubling it would make it 10 mm. Hg and the intraocular pressure would rise from 15 mm. Hg to 20 mm. Hg. Similarly, if three-fourths of the holes were obliterated intraocular pressure would rise to 30 mm. Hg. Such conditions probably arise in cases of secondary or narrow-angle glaucoma.

Changes in the diameter of the individual holes produce very large changes in C, because the diameter is raised to the fourth power. If the diameters were decreased by ½ the facility of outflow would be decreased by 1/16, the pressure drop would increase 16 times, giving an intraocular pressure of 90 mm. Hg. Similarly, if the diameters were decreased by one-quarter, the intraocular pressure would rise to

27 mm. Hg. If this is compared with blockage of the number of holes described earlier, it will be noted that the increase in pressure resulting from obliterating three-quarters of all the holes (30 mm. Hg) is about equivalent to decreasing each hole only one-quarter in diameter (27 mm. Hg).

It is obvious that according to Poiseuille's law a small change in the diameter of the holes produces large changes in the rate of flow. Conversely, the condition of wide-angle glaucoma with increased pressure can be caused by a diminution of hole size too small to be detected histologically. This probably explains why it has been so difficult to show the pathological basis for open-angle glaucoma. Bárány [14] has called attention to this in pointing out that only a thin coating of hyaluronic acid is needed in order to produce considerably increased intraocular pressure.

It is necessary here to interject some notes of caution. Poiseuille's law is strictly applicable when two important conditions are met. The flow must be laminar, and the tube should be cylindrical. The criterion of laminar flow is determined by the application of Reynold's number. It may easily be shown that substitution of the above values results in a value for Reynolds' number [15] clearly indicating laminar flow. The criterion of a cylindrical hole is based on the relation that the length should be considerably greater than the diameter. Even our best assumptions do not seem to meet this condition. However, it has been shown that Poiseuille's law applies to filter beds [16] which are composed of a network of interstices and do not have tubular holes.

These hydrodynamic laws of flow apply to the flow of aqueous all along its path from the anterior chamber to the episcleral venous system. On the anterior chamber side of Schlemm's canal the corneoscleral and uveal trabecular spaces would have to be considerably reduced in size before they would offer sufficient resistance to cause the pressure rises found in an open-angle glaucoma. On the other side of Schlemm's canal the collector channels might be a locus of increased resistance. It is of interest to apply briefly Poiseuille's law to these structures. The dimensions of the collector channels have been estimated by Theobald [17] to be 30μ to 165μ in length; usually elliptical in cross section, giving axes of 5μ to 50μ and 30μ to 165μ, and numbering approximately 30. If we assume an average length of 100μ, then we may apply Equation 8, remembering that L is increased five times, to give

$$ND_c^4 = 1 \times 10^{-11} \text{ cm.}^4 \qquad (12)$$

With substitution of 30 for the number of channels, we find that the average diameter would have to be about 8μ. This would suggest that the collector channels would have to be considerably narrowed before they would contribute significantly to the outflow resistance.

It is of interest to compare this result with the computation of Ascher,[18] who applied Poiseuille's law to the flow through the collector channels from Schlemm's canal. His calculations showed that, according to values he used, the flow was about 20 mm.^{3} per minute, which is some 10 times greater than normal flow. His result again indicates that the collector channels are probably not a site of much resistance in the normal eye.

Such computation and applications of Poiseuille's law of flow appear useful in explaining some of the obscurities of glaucoma. Only further research will give quantitative aspect to the factors influencing the rate of outflow of the aqueous humor.

Summary

Application of Poiseuille's law to the outflow of aqueous humor reveals several interesting conclusions.

The major resistance to the outflow of the aqueous in the normal eye is due to a low-porosity tissue barrier averaging about one hole (2μ in diameter) every 0.01 mm.^{2}

A decrease in the diameter of these holes, a change too small to be detected histo-

logically, can account for "open-angle" glaucoma.

The location of this normal barrier to outflow probably occurs in the very near vicinity of Schlemm's canal on the anterior chamber side.

The high porosity of the uveal and corneoscleral trabeculae and the collector channels indicates that little resistance to flow is normally encountered at these sites. Only if greatly narrowed or blocked may they offer sufficient resistance to account for glaucoma.

A single patent hole 12μ in diameter is sufficiently large by itself to give a normal facility of outflow.

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Centrifugal Influence upon the Electroretinogram

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The existence of fibers in the optic nerve which convey efferent impulses from the higher centers to the retina has been a matter of interest and discussion for many years. Histological evidence for these fibers and for the retinal cellular components of such an efferent system has been provided by Dogiel,[1] Cajal,[2] Johnston,[3] and Polyak.[4] Physiological evidence has been noted by Arey,[5] who discussed the influence of such elements upon retinal light and dark adaptation. The importance of such a system in dark adaptation has been also mentioned by Pfeifer.[6] Monakow[7] described, as a result of animal experiments, the existence of a centrifugal pathway.

Polyak,[8] more recently, in speaking of "the mechanisms of facilitation or inhibition," states that "a structural arrangement whose function seems to be an interference with the synapses between other neurons is exemplified by the horizontal and centrifugal bipolars of the retina . . . the undoubted anatomical relationship mentioned demands an acceptance of some kind of influencing, (by the horizontal cells) most likely of the photoreceptor-bipolar relationship." He then conjectures that these anatomical findings may represent a mechanism for inhibition of rod and cone function, due to change in threshold, or for differentially blocking of rods in daylight vision. The centrifugal bipolar cells are considered to be able to influence cone-afferent bipolar transmission.

Granit[9] has been able to inhibit and facilitate spontaneous and evoked retinal potentials by electrical stimulation of the mesencephalic reticular substance, and he considers this to be evidence of centrifugal fibers. Walter[10] has demonstrated efferent fibers terminating in retinal blood vessels.

Motokawa and Ebe[11] demonstrated that antidromic stimulation of the optic nerve depressed the sensitivity of the retina and pointed out that the electrical response of the retina is dependent upon the general condition of the animal. Hartline[12] has demonstrated antidromic inhibition in the eye of Limulus. Barany and Hallden[13] showed that central nervous system depressants (alcohol and barbiturates) affected retinal interrelationships.

Dodt[14] found that he could elicit a delayed retinal spike by shocking the contralateral optic tract of a rabbit. He believes this is evidence for the existence of a true centrifugal function.

In this study an attempt is made to clarify the existence and role of centrifugal fibers.

Methods

Adult cats and Java monkeys were used in this study. The technique on human material will be fully described elsewhere.[15]

In cats, tracheal cannulae were introduced, with use of ether anesthesia, and one of the femoral or subclavian veins was cannulated. After all surgical sites were thoroughly infiltrated with procaine, the animals were permitted to recover and were

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From the Division of Electrophysiology, Department of Research, New York Eye and Ear Infirmary and the Albert Einstein College of Medicine, Department of Ophthalmology.

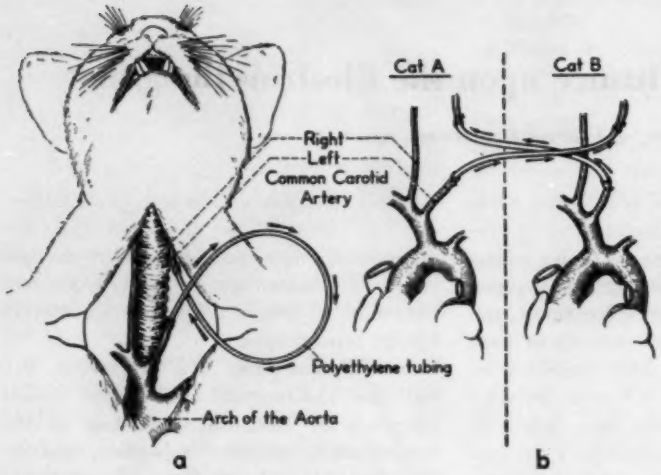


Fig. 1.—Technique of carotid cross perfusion. In order to avoid prolonged brain anoxia, each cat was first prepared as shown in (*a*), following which each tube was cut at its center and cross connected as shown in (*b*). This resulted in commingling of the circulations of the two animals.

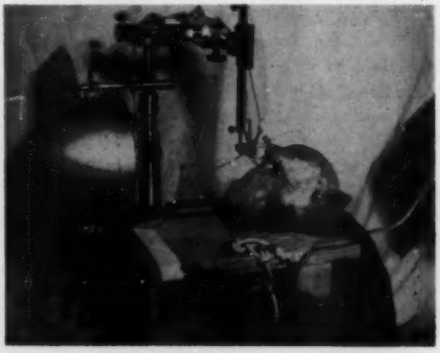
paralyzed with succinylcholine or curare. Artificial respiration and continuous intravenous drip of saline and dextrose maintained the preparations for 10 to 12 hours without appreciable signs of deterioration. The animal was placed in a prone position in an especially designed headholder, and silver-silver chloride spring-ball-type electrodes in saline-soaked cotton were gently placed or sutured against the cornea of each eye. In some cases the nictitating membrane was sutured to the inner canthus to avoid interference with the record. A Grass No. 5 Polygraph provided direct-writing ink records, and a Grass preamplifier P 5R fed a Dumont oscilloscope Type 333 for photographic recording. The obtained tracings were photographically superimposed and printed in sets of five consecutive sweeps.

High-frequency electrical stimulation of the reticular formation was accomplished acutely by suction removal of the medial part of the cerebellum and positioning of a stimulating electrode posterior to the quadrigeminal bodies, under direct vision. In chronic experiments the electrode was driven stereotaxically through the cerebrum.

For the purpose of unilateral optic nerve section, craniotomies were performed on cats and monkeys, allowing gentle retraction of one of the frontal lobes until the optic chiasm became fully exposed. A length of surgical silk was then looped around one of the optic nerves just distal to the chiasm and the brain was released. While both ERG's were monitored with a one-per-second flash delivered to both eyes, the silk loop was sharply pulled, resulting in a section of the optic nerve.

For cross perfusion experiments [16] a pair of cats, similar in body weight and age, were anesthetized and their left common carotid arteries were exposed. After surgical ex-

Fig. 2.—Monkey in position in recording chair, showing corneal electrodes in place, suture line from optic nerve section surgery, and respirator tube. Clear tube at right is cannula leading to vein, providing for saline and dextrose administration and, by means of a three-way stop-cock, a means of administering drugs. The Erlenmeyer flask in the center contains saline for moistening the electrodes.



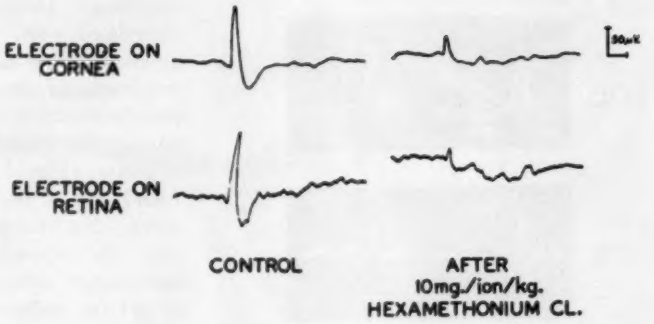


Fig. 3.—Simultaneous recordings from each of the two eyes of a cat before and after intravenous administration of hexamethonium. The lower tracings were made with an electrode on the surface of the retina in an eviscerated eye; the upper ones, from a corneal electrode, showing no major variations between the techniques.

posure of the brain stem of the "donor" cat, 10,000 units of heparin sodium was administered to each cat. After a delay of three hours, to allow for complete heparin effect, a polyethylene tube, about 40 cm. long, was introduced into the artery of each cat, as shown in Figure 1*a*. This procedure reduced cerebral blood flow for less than one minute. No appreciable damage to the brain due to anoxia is to be expected in this time. When both cats were prepared in this fashion, they were placed on a common animal table and connected to a common positive pressure respirator. Either succinylcholine or section of the spinal cord at C-1 (*encéphale isolé*) paralyzed the animals while their recovery from ether anesthesia was awaited. At this point both polyethylene tubes were cut and cross connected in a fashion shown in Figure 1*b*. Cross circulation was verified after the experiment with the help of dyes.

In the monkey studies, similar techniques were used; Figure 2 shows an animal in the recording chair with corneal electrodes in place. A Grass H730×8 photostimulator supplied the common light excitation to both eyes.

Since tracings recorded from the cornea and retina are alike for all practical purposes when condenser-coupled amplifiers are used (Fig. 3), ERG's in this report are those recorded from the corneal surface.

All tracings were performed after a 10-minute period of dark adaptation. Pupils were maximally dilated with atropine drops to eliminate variation in pupil size as a source of error.

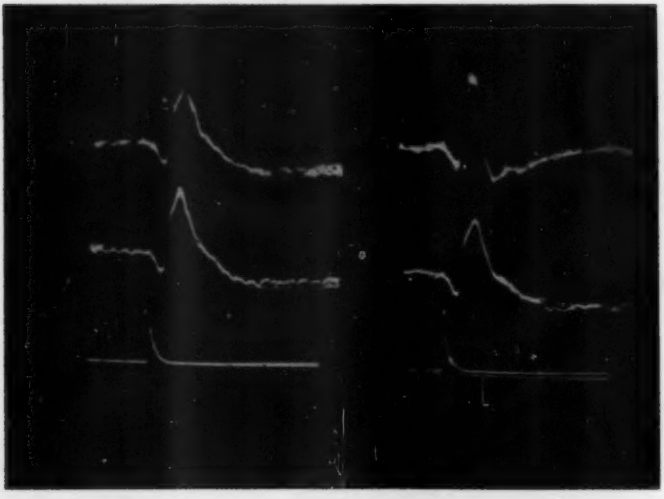


Fig. 4.—Effect of unilateral optic nerve section on ERG of cat. Multiple sweep tracings of both eyes before and immediately after section of nerve of left eye (top pair of tracings). Lowest tracings represent light stimulus.

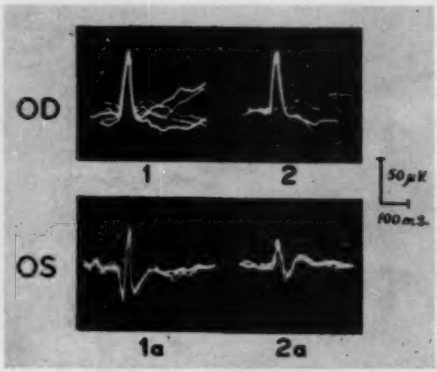


Fig. 5.—Effect of intravenous injection of pentylenetetrazole upon the ERG in a cat with sectioned optic nerve in right eye. Marked diminution in amplitude of response in eye with intact nerve. No change in eye with sectioned nerve.

Results

An immediate increase in the ERG amplitude followed section of the optic nerve (Fig. 4), if the animal was under light anesthesia. In deeply depressed animals no increase was noted. Another series of cats was prepared in which unilateral optic nerve section was performed at intervals of time varying from minutes to weeks prior to recording. Drugs were injected into a cannulated vein. Hexamethonium, a ganglionic blocking agent, markedly reduced the amplitude of the ERG. Strychnine and pentylenetetrazol (Metrazol), central nervous system stimulants, also diminished the response (Fig. 5). This diminution was found only in the eye with the intact optic nerve. No change was noted in the eye with the sectioned nerve. In cats with undisturbed optic nerves both eyes reacted as did the unilateral intact eye in the cats with one optic nerve sectioned.

Pentobarbital and ether, central nervous system depressants, caused an increase in the ERG amplitude in the intact eye only, with no change noted in the response on the side of the sectioned nerve (Fig. 6).

These drugs were dropped, in varying concentrations, upon the surface of the exposed cat and human retina.[15] No significant effect was noted.

The fact that alteration of blood pressure is not the cause of these changes is shown in Figure 7. Blood pressure drops due to pentobarbital and hexamethonium are about equal, but while pentobarbital increases the

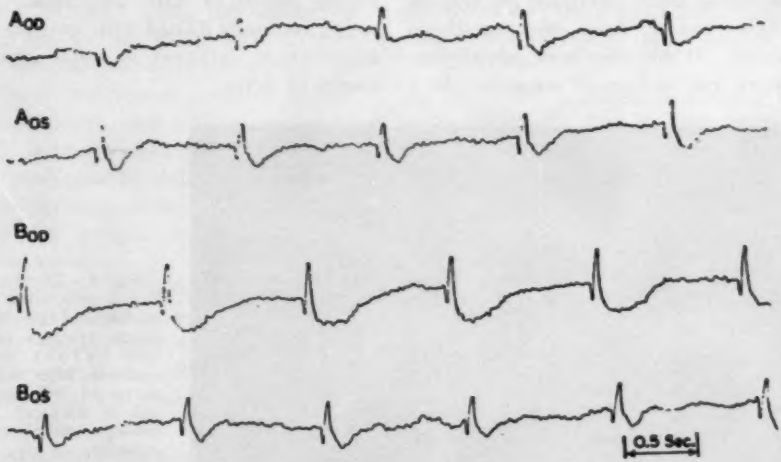


Fig. 6.—Effect of intravenous injection of pentobarbital upon the ERG in a Java monkey with sectioned optic nerve in left eye. Marked increase (*B*, O. D.) in response in eye with intact nerve. No change in eye with sectioned nerve.

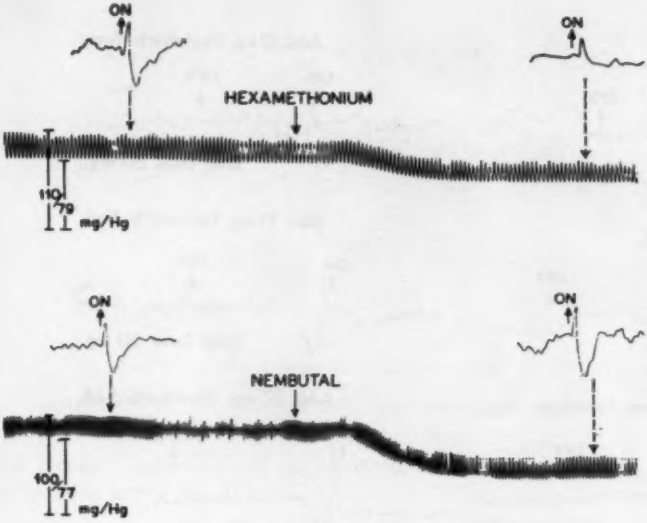


Fig. 7.—Simultaneous recording of ERG and blood pressure of two cats, showing increase in ERG amplitude following administration of pentobarbital intravenously and decrease following hexamethonium, in spite of greater drop in blood pressure due to pentobarbital.

ERG hexamethonium decreases it, provided the optic nerves are intact.

It was also interesting to note that spontaneous action potentials as described by Apter [17] following *d*-lysergic acid diethylamide (LSD) administration in cats occurred only in eyes with intact nerves (Fig. 8). These findings will be described in detail elsewhere.[18,19]

Figure 9 shows the effect of anesthesia on the ERG. The amplitude of the response increases as the level of anesthesia increases. Noell [20] has also noted this finding.

Electrical high-frequency stimulation of the bulbar reticular formation reduced the ERG amplitude; this effect lasted for over two minutes, although the stimuli bursts never exceeded eight seconds (Fig. 10).

It has been shown that stimulation of this area also inhibits dendritic activity [21]; however, the long-lasting after-effect cannot be explained by cortical neurons inhibiting apical dendrites.

In order to determine the possible role of neurohumors, cross perfusion experiments were set up. The reticular formation of one animal was stimulated, and, while the ERG of the stimulated cat (donor) diminished immediately, changes in the ERG of

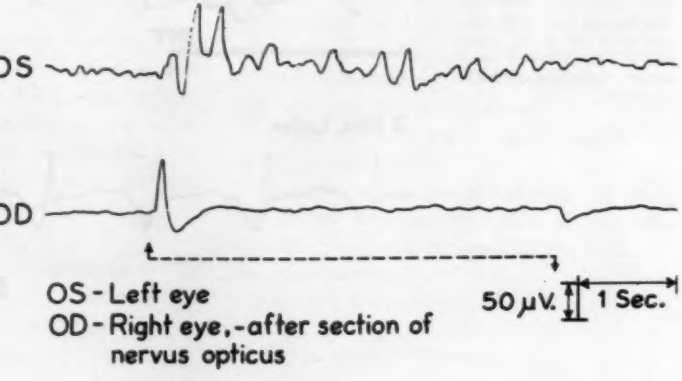


Fig. 8.—Effect of intravenous injection of LSD-25, 100μg. per kilogram, upon the ERG of a cat with sectioned optic nerve, O. D. Spontaneous activity bursts following single sustained light stimulus (dotted line). Similar findings sometimes occurred in deeply depressed animals.

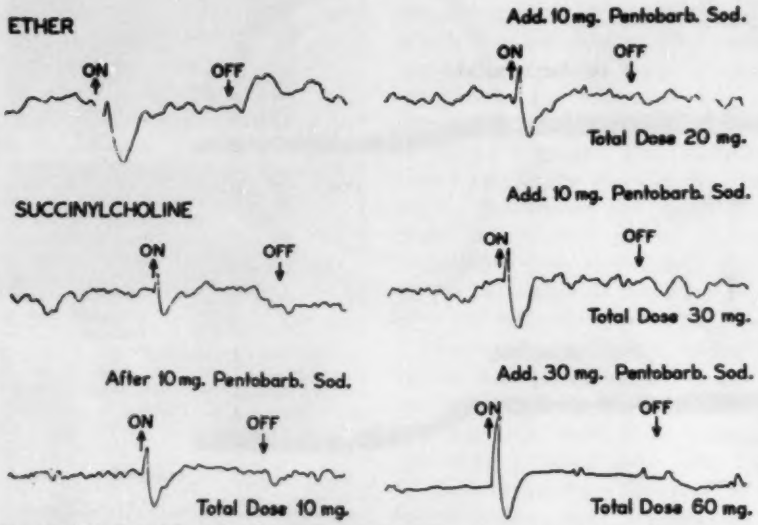


Fig. 9.—Effect of ether anesthesia, succinylcholine, and serially increasing doses of intravenous pentobarbital upon the ERG of a cat, showing increasing amplitude of response after repeated doses of pentobarbital.

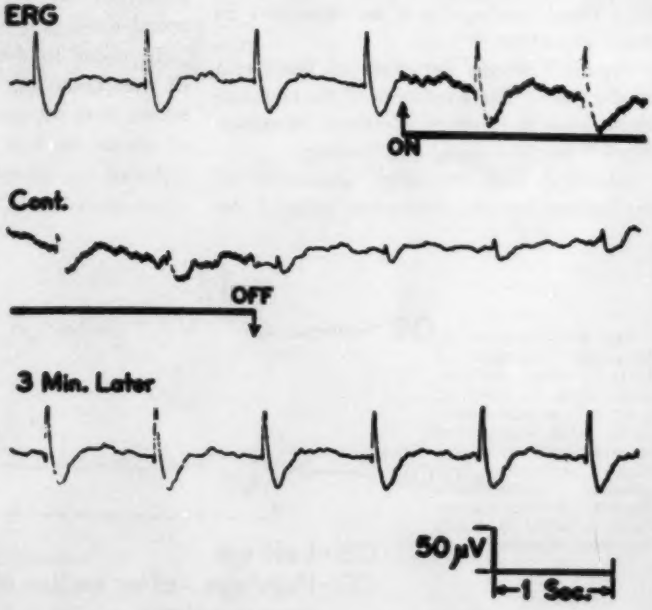


Fig. 10.—Effect of 8 volt sinusoidal 120 cps stimulation of reticular substance of a cat upon the ERG. Marked temporary reduction of ERG amplitude.

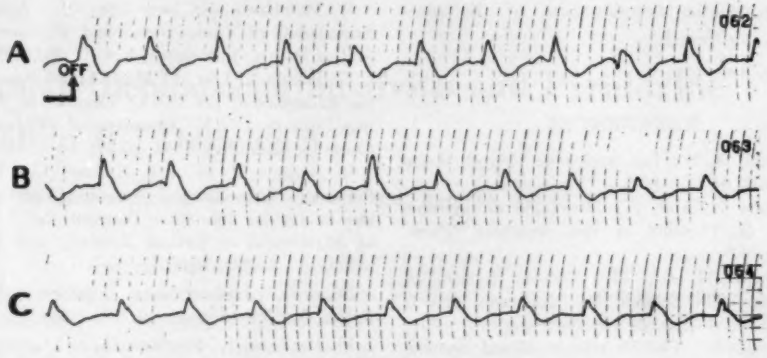


Fig. 11.—Consecutive tracings of ERG of recipient cat of a cross perfusion pair. Termination of electrical stimulation of donor cat marked at top left. Responses to one-per-second stimuli, showing diminution of ERG approximately 16 seconds following stimulus.

the second (recipient) cat occurred about 40 seconds later (Fig. 11).

Comment

The abolition by optic nerve section of the effect of certain drugs upon the ERG is evidence for the existence of centrifugal fibers in the optic nerve. In addition, we feel that it is possible to hypothesize upon the basis of these findings that there exists in the brain a center which controls retinal function, whose activity we can measure by its effect upon the ERG. This center, stimulated physiologically by retinal activity, or, in these experiments, by hexamethonium, central nervous stimulants, or electricity acts to inhibit retinal activity. Central nervous system depressants reduce the activity of this inhibitory center and thereby increase retinal activity.

Section of the optic nerve interrupts the efferents of the center. This causes an immediate increase in the ERG, due to lack of central inhibition. Section of the nerve also abolishes the action on the ERG of drugs, since the center, which is the site of action of the drugs, now has no way of controlling the ERG.

This type of center is conceived of as a type of feedback control, regulating the rate and/or intensity of retinal activity and controlling dark adaptation.

The cross perfusion experiments seem to imply the existence of a slower-, longer-acting neurohumoral system whose action could be on the cephalic center, the retina, or both.

Further experiments utilizing cross perfused cats with unilateral optic nerve section are now in progress in the hope of eliciting information on the relationship between the neuronal and neurohumoral factors in the visual system, while chronic cephalic lesions and stereotaxically implanted electrodes may give us more information on the anatomical location of this inhibitory center.

Summary

The ERG was found to increase in amplitude following optic nerve section or administration of barbiturates.

The ERG was found to decrease in amplitude following administration of pentylenetetrazol (Metrazol), hexamethonium, or electrical reticular stimulation.

Section of the optic nerve eliminated the effects of the drugs.

In cross perfusion experiments stimulation of the reticular formation of one animal also produced changes in the ERG of the other animal.

It is felt that these findings are evidence for the existence of centrifugal fibers in the optic nerve.

A hypothetical explanation of the phenomena is offered.

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Angular Blepharoconjunctivitis and Pyridoxine (Vitamin B_6) Deficiency

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Introduction

Symptoms due to pyridoxine (vitamin B_6) deficiency in experimental animals have been known to a certain extent. As to the symptoms in man, Mueller [1] was the first who, by giving deoxypyridoxine, developed them. Since then, Schreiner,[2] Vilter,[3] and other researchers have reported on this subject. In the field of ophthalmology, however, experimental reports on this subject are very few and the symptoms are still indefinitely known.

We made the following pyridoxine-deficiency experiments with rats and rabbits in order to observe both general and ocular changes and to compare the affections to those found in human eyes.

Experimental Method

As experimental animals 25 rats and 25 rabbits were used; in addition, 5 animals of each kind were prepared for controls.

1. *Rats.*—They were young and rather weak, from 40 to 70 days old, and weighed from 50 to 100 gm.

Feeding: The feeding box was 23 cm. long, 23 cm. wide, and 20 cm. deep, made of wire netting, with a 2 cm.-high foot attached. The box was put into a 3 cm. deep tin box in such a way as to prevent the rats from eating their excreta. Water supply was not limited at all.

Food: According to Bowles' diet for rats [4] and Shwartzman's diet for hamsters,[5] the following mixture was used as pyridoxine-deficiency food.

The basal diet consisted of Hammersten's refined casein (25%), sucrose (61%), McCollum's combined salts (5%), and bean oil (9%); it was softened with water to a paste-like consistency and placed in such a way that the rats could eat freely, at their wish. The additional vitamin quantity per 100 gm. of basal diet was as follows:

Thiamin (vitamin B_1)	0.4 mg.
Riboflavin (vitamin B_2)	1.6 mg.
Calcium pantothenate	2.0 mg.
Nicotinic acid	1.0 mg.
Inositol	10.0 mg.
Choline	100.0 mg.
Biotin	0.002 mg.
Menadione	1.0 mg.
Folic acid	0.01 mg.
Liver oil	1 cc.
(vitamin A, 1500 I. U.; vitamin D, 150 I. U.)	
Ascorbic acid (vitamin C)	1.0 mg.

Later pyridoxine (0.4 mg.) was added to the diet of the control animals.

2. *Rabbits.*—They were young and rather weak, from 20 to 60 days old, and weighed from 400 to 1000 gm.

Rabbits are, speaking in general, gentle and big enough to make it easy to observe the ocular changes. When the mixed food is being fed, as Sato [6] and Yamada [7] reported, the rabbits at the weaning period (20 to 30 days old) are preferred, for they have no hesitation in eating the food. Sometime after the weaning period the rabbits are so accustomed to normal diet that it is not easy to change the food to the mixed one. Some of the rabbits, however, got accustomed to the mixed food, maybe because the mixed food was given only when they were hungry.

Feeding: The feeding box was 47 cm. long, 40 cm. wide, and 36 cm. high and was made of tin plate. The side-walls and the floor of the box were covered with wire net. The top was freely opened and closed. The

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foot of the box was 3 cm. high. The box was put into a 5 cm.-deep box made of tin plate, in which all the excreta was kept. The food, which was prepared each morning, was given once a day.

Food: According to Wooley's method [8] for rabbits, the following mixed food was given. The basal diet, consisting of Hammersten's casein (25%), powdered glucose for injection (51%), cellophane (15%), bean oil (5%), and McCollum's combined salts (4%), was mixed with various vitamins recommended in Tappan's and in Yamada's method.[9] The quantity of the vitamins per day for one rabbit was as follows:

Thiamine	1.0 mg.
Riboflavin	1.0 mg.
Nicotinic acid	2.0 mg.
Adenylic acid	2.0 mg.
Folic acid	0.5 mg.
p-Aminobenzoic acid	25.0 mg.
Biotin	0.02 mg.
Choline	25.0 mg.
Calcium pantothenate	3.0 mg.
Liver oil (vitamin A, 750 I. U.; vitamin D, 75 I. U.)	0.5 cc.
Ascorbic acid	25.0 mg.
Vitamin E	1.5 mg.
Vitamin K	9.0 mg.
Vitamin P	20.0 mg.

Later pyridoxine (1.0 mg.) was added in the diet of the control rabbits.

Examination.—Body weight and general condition of the experimental animals were carefully examined every day. As for the ocular examinations, focal illumination, transillumination, and microscopic corneal examinations by slit lamp were made. In the rabbits, pyridoxine in urine, and in the rats, pyridoxine in organs was quantitatively analyzed. Pyridoxine load test and recovery test were also performed. Histopathologic examination was done chiefly on the visual organs. The histologic sections were fixed in 10% formalin, or sometimes in Bouin fixing fluid, and then were embedded, chiefly in paraffin and celloidin. The specimens were stained with hematoxylin and eosin and Van Gieson's stain.

Results

1. *Experimental Data on Rats.*—The 25 young rats weighing 50 to 100 gm. had their hair stained in not later than from 20 to 30 days. The ears became congested and swollen, red-brown scabs were formed, and they finally became necrotic. The nose, congestion and humidity were seen, necrotic ears naturally fell off. Around the while on the legs some seborrheic scales were observed. The weight showed its maximum in 20 to 40 days and then it decreased gradually. As the weight began to decrease, the ocular changes took place.

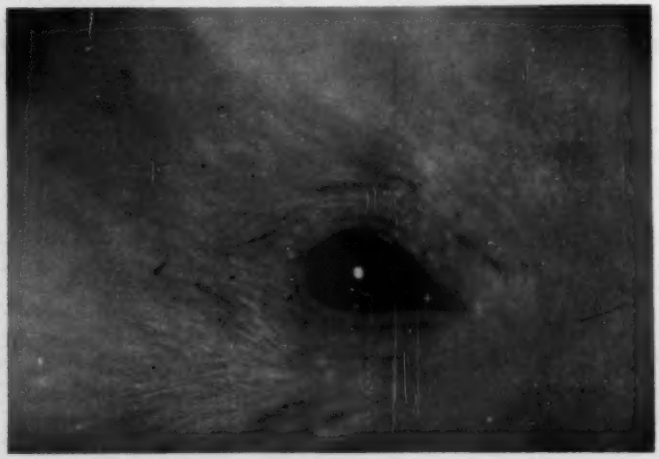

Fig. 1. — Congestion and humidity of the eyelid and its margin in a rat. (Reprinted from Mikami, H.: *Acta ophth. japon.* 60:1236, 1956.)

The ocular changes were congestion of the margo palpebralis, falling-off of hair around the eyelid, and congestion of the eyelid. The margo palpebralis with congestion and humidity had a red-brown scab formed at the nasal angle, except in one case that showed redness, humidity, and even the scab-formation at the temporal angle. In some cases both the eyelid and its margin showed strong congestion and humidity like a true blepharitis angularis (Fig. 1). The limbus corneae was congested, and a slit-lamp examination showed a neovascularization that ran to the central part of the cornea from the limbal vascular loops. Histopathologic examinations showed, in all cases, hyperkeratosis on the skin of the eyelids. In most cases the blood vessels were dilated and the lids were edematous, although neither palpebral epithelium was affected markedly nor had the subepithelium a marked cell infiltration. However, in one case, a slight infiltration, chiefly of plasma cells, was seen. And in another case lymphocytes, neutrophils, and plasma cells were infiltrating diffusely to the margin and the subcutaneous tissue of the eyelid. In the subcutaneous tissue of both conjunctiva palpebrae and conjunctiva bulbi, an infiltration of lymphocytes, plasma cells, and

Fig. 2.—Cellular infiltration at the lid margin and subcutaneous tissue.

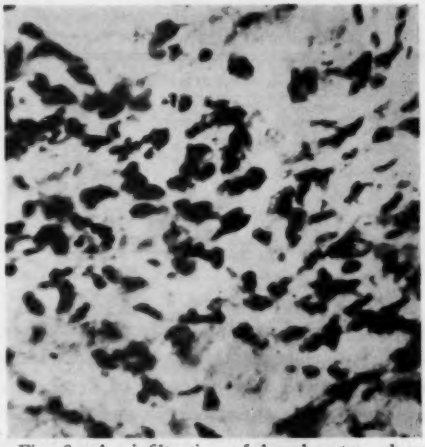

Fig. 3.—An infiltration of lymphocytes, plasma cells, and monocytes (high magnification).

monocytes forming a conglomeration was seen (Figs. 2 and 3). A dilation of the limbus vessels, around which lymphocytes infiltrated to a high degree, was observed in the cornea. Corneal epithelial cells were forming vacuoles in the protoplasm. The upper region of the corneal stromal lamella had a corneal neovascularization that ran to the central part of the cornea. An infiltration, chiefly of neutrophils, was seen in the region of neovascularization and in the corneal stromal lamella at the limbus. When the recovery test was given, by giving pyridoxine, however, those general symptoms and ocular changes mentioned above almost all disappeared; even a histological picture showed all to be normal.

2. *Experimental Data on Rabbits.*—The 25 young rabbits, each of which weighed 500 to 2000 gm., had general symptoms such as brown stain, loss of gloss and roughness of the entire fur, and even loss of hair after 10 to 25 days. The weight was increasing during the first 15 days. Thereafter, however, it began to decrease. As to ocular changes, injection and humidity at the margo palpebralis, congestion of the conjunctiva palpebrae, and discharge from the eyes into the nasal angle were seen. In the corneas, in most cases, dilation and injection of the limbus vessels showed, and some of them showed even a neovascularization.

TABLE 1.—*Pyridoxine in the Urine of Pyridoxine-Deficient Rabbits*

Rabbit No.	Pyridoxine, μg. %: Before Experiment	5th Day	10th Day	15th Day	20th Day	25th Day
5	22.8	20.6	20.0	17.6	15.8	9.3
8	22.5	17.3	17.2	11.4	8.3	8.4
12	20.0	19.2	15.5	12.4	12.1	11.3
15	17.6	16.0	13.5	12.0	9.1	9.0
Controls						
26	20.0	19.3	18.2	17.8	16.4	16.9
27	19.3	19.6	18.7	17.9	17.1	19.0

Iris, lens, and fundus oculi, however, showed no changes. Histopathologic examinations showed a high degree of keratinization in the margo palpebralis and the eyelid skin: The epithelium showed no special changes, while the subepithelial tissue was edematous owing to the dilation of the vessels. In most cases just below the epithelial layer a picture of chronic inflammation appeared, showing an infiltration of lymphocytes, plasma cells, and monocytes. Some cases showed neovascularization in the upper region of the corneal stromal lamella. Those rabbits that came through the recovery test and had ocular changes showed so much improvement that the histopathologic picture showed no significant pathological changes.

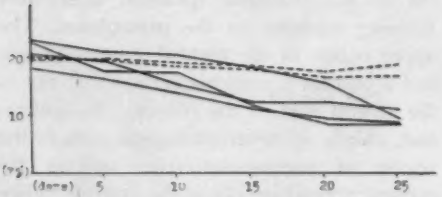

Fig. 4.—Curve of pyridoxine quantity in the urine of pyridoxine-deficient rabbits. Solid lines, deficient rabbits; broken lines, controls.

Quantitative Analysis of Pyridoxine, Riboflavin, and Nicotinic Acid

In order to know the relationship between the state of pyridoxine deficiency and that of riboflavin and nicotinic acid deficiency, a quantitative analysis was performed as follows: The analysis of pyridoxine was done by Fujino's fluorescent method [10]; that of riboflavin, by Yagi's fluorescent method,[11] and that of nicotinic acid, by comparison color analysis with bromcyanin and *p*-aminoacetophenone.[12] In rabbits, the quantitative analysis of pyridoxine, riboflavin, and nicotinic acid was done with urine, while in rats the analysis of pyridoxine and riboflavin was done with organs (liver and kidney).

TABLE 2.—*Pyridoxine in the Organs of Pyridoxine-Deficient Rats*

Rat No.	Pyridoxine, μg/Gm.: Liver	Kidneys
5	0.5	0.3
8	0.2	0.4
11	0.4	0.3
19	0.6	0.5
Controls		
26	1.1	1.5
27	1.9	1.0

Pyridoxine quantity in rabbit urine was analyzed as Table 1 and Figure 4 show; it was observed that the excretion of pyridoxine in urine, in all cases, was remarkably low after 10 to 15 days in comparison with the controls. Pyridoxine in the organs of rats also was less than in those of the controls, as shown in Table 2. In like manner, riboflavin quantity in the urine of pyridoxine-deficient rabbits, as shown in Figure 5, and nicotinic acid quantity, as shown in Figure 6, were somewhat lower as compared with the controls. Riboflavin quantity in the organs of rats was measured as shown in Table 3, and in the liver the measurement showed a decreasing tendency, as compared with the controls. It has been proved by the

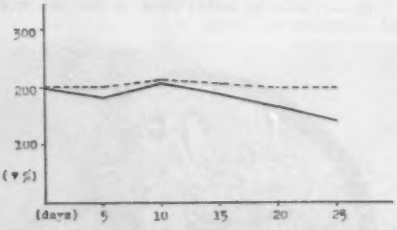

Fig. 5.—Curve of pyridoxine quantity in the urine of a pyridoxine-deficient rabbit. Solid line, deficient rabbit (Rabbit 15); broken line, control (Rabbit 27).

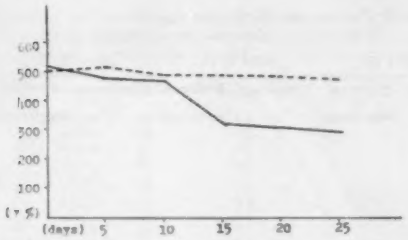

Fig. 6.—Curve of nicotinic acid quantity in the urine of a pyridoxine-deficient rabbit. Solid line, deficient rabbit (Rabbit 5); broken line, control (Rabbit 28).

experimental results mentioned above that in the urine and organs of pyridoxine-deficient animals excretion quantity of pyridoxine is lower than in the controls. In other words, the animals were certainly in need of pyridoxine. The same holds true with riboflavin and nicotinic acid in urine and organ.

As a further experiment we gave a loading test to the pyridoxine-deficient rabbits and obtained the following results, as shown in Table 4; pyridoxine quantity in the urine of the controls increased to 29.9μg. to 32.4μg. after three hours and then began to decrease. After 12 hours the quantity was as much as 1.8μg. to 2.9μg., and the excretion rate was 5.1% to 5.4%. However, in the pyridoxine-deficient animals, the quantity increased only to 1.1μg. to 1.2μg. after three hours and the rate was 0.2% to 0.3%. As mentioned already, there was a great difference between the pyridoxine-deficient animals and the controls, and it became self-evident that the former had disturbance in pyridoxine metabolism.

TABLE 3.—*Riboflavin in the Organs of Pyridoxine-Deficient Rats*

Rat No.	Pyridoxine, μg/Gm. Liver	Kidneys
3	16.9	55.5
8	19.7	24.8
11	17.0	6.6
19	11.2	21.1
	Controls	
26	27.8	35.5
27	46.4	14.9

Inoculation of Hemophilus Duplex into the Conjunctiva Palpebrae of Pyridoxine-Deficient Animals

It has been said that blepharoconjunctivitis angularis, clinically speaking, is a manifestation of Hemophilus duplex (Morax-Axenfeld bacillus) infection. Some ophthalmologists of late, however, report that pyridoxine deficiency also has something to do with the disease. In order to prove the relationship between H. duplex and pyridoxine deficiency we made the following inoculation tests in the pyridoxine-deficient animals.

Inoculation Material: Two kinds of H. duplex strains that were obtained from a case of typical blepharoconjunctivitis angularis and cultured were used. They are Niigata strain (given by the department of ophthalmology, Niigata University) and Hirosaki strain (obtained and cultured in our department).

1. *Inoculation in Rats.*—Hirosaki strain of H. duplex from the colony was put into the saccus conjunctivae of the right eye, and

TABLE 4.—*Pyridoxine Load Test in Rabbits*

Rabbit No.	Weight, Gm.	Pyridoxine, Mg.	Pyridoxine Excreted, μg. Before Loading	After 3 Hr.	After 6 Hr.	After 9 Hr.	After 12 Hr.	Pyridoxine Excreted, %
18	830	1	0.7 (8)	1.2 (10)	0.9 (7)	0.6 (8)	0.5 (6)	0.3
20	800	1	0.5 (9)	1.1 (5)	0.9 (6)	0.4 (6)	0.3 (5)	0.2
			Controls					
28	810	1	1.0 (9)	29.9 (12)	17.4 (10)	3.4 (7)	1.8 (8)	5.4
29	790	1	1.3 (8)	32.4 (8)	14.1 (7)	3.2 (5)	2.9 (8)	5.1

* The size of the urine sample, in cubic centimeters, is given in parentheses.

TABLE 5.—*H. Duplex Inoculation Test in Pyridoxine-Deficient Rats* *

Rat No.	After 24 Hr.		After 48 Hr.		After 72 Hr.		After 96 Hr.		After 120 Hr.	
	Symptoms	Evidence of Bacterium	Symptoms	Evidence of Bacterium	Symptoms	Evidence of Bacterium	Symptoms	Evidence of Bacterium	Symptoms	Evidence of Bacterium
17	—	—	—	—	—	—	—	—	—	—
21	—	—	—	—	—	—	—	—	—	—
23	Congestion at the palpebral conjunctiva and lacrimation	(Culture) +	—	—	—	—	—	—	—	—
24	—	—	—	—	—	—	—	—	—	—
25	—	—	—	—	—	—	—	—	—	—
					Controls					
26	—	—	—	—	—	—	—	—	—	—
27	—	—	—	—	—	—	—	—	—	—
28	—	—	—	—	—	—	—	—	—	—
29	—	—	—	—	—	—	—	—	—	—
30	—	—	—	—	—	—	—	—	—	—

* Inoculation was made into the saccus conjunctivae of the right eye.

the left eye was under observation as the control.

Experimental Data: As Table 5 shows only Rabbit 23 had a slight congestion at the conjunctiva palpebrae, eye discharge, and lacrimation. H. duplex was found by culture, although after 48 hours the congestion disappeared and H. duplex was not found. In the other four, inoculation caused no changes at all and H. duplex was not found either in the smear specimen or in the culture; this was also the case in the controls, and H. duplex was not found at all.

2. *Inoculation in Rabbits.*—Niigata strain of H. duplex was inoculated in the same method as was done to rats.

Experimental Data: As Table 6 shows, H. duplex was found in Rabbit 16 up to the 72d hour and in Rabbit 21 up to the 48th hour both in the smear specimen and in the cultured specimen taken from eye discharge. Thereafter, the clinical manifestations disappeared and all was as it had been before inoculation, and the bacillus was not found.

Among the controls, Rabbit 27 had a slight congestion at the conjunctiva palpebrae and eye discharge 24 hours after inoculation, and H. duplex bacillus was found in the culture from the eye discharge. More than 24 hours later, however, H. duplex bacillus was never found.

TABLE 6.—*H. Duplex Inoculation Test in Pyridoxine-Deficient Rabbits*

Rabbit No.	After 24 Hr.		After 48 Hr.		After 72 Hr.		After 96 Hr.		After 120 Hr.	
	Symptoms	Evidence of Bacterium	Symptoms	Evidence of Bacterium	Symptoms	Evidence of Bacterium	Symptoms	Evidence of Bacterium	Symptoms	Evidence of Bacterium
13	—	—	—	—	—	—	—	—	—	—
14	—	—	—	—	—	—	—	—	—	—
16	Congestion at the palpebral conjunctiva and eye discharge	(Smear) +	Slight congestion of the palpebral conjunctiva	(Smear) +	—	(Culture) +	—	—	—	—
19	—	—	—	—	—	—	—	—	—	—
21	Congestion at the palpebral conjunctiva and eye discharge	(Smear) +	—	(Culture) +	—	—	—	—	—	—
					Controls					
26	—	—	—	—	—	—	—	—	—	—
27	Congestion at the palpebral conjunctiva and eye discharge	(Culture) +	—	—	—	—	—	—	—	—
28	—	—	—	—	—	—	—	—	—	—
29	—	—	—	—	—	—	—	—	—	—
30	—	—	—	—	—	—	—	—	—	—

TABLE 7.—*Pyridoxine in the Urine of Patients with Blepharoconjunctivitis Angularis*

Case No.	Sex	Age, Yr.	Pyridoxine in Urine, μg. %	Evidence of H. Duplex
1	female	79	3.3	
2	female	56	2.8	
3	female	40	2.0	
4	male	22	3.8	
5	female	14	3.3	
6	male	84	1.6	
7	female	51	3.2	
8	female	30	1.0	
9	female	59	1.6	
10	female	32	3.4	
11	male	68	2.2	
12	female	65	1.4	+
13	female	25	2.3	
14	female	7	2.4	‡
15	female	16	1.5	‡
16	female	29	2.9	
17	male	17	2.8	
18	female	67	3.5	
		Controls		
1	male	28	4.4	
2	male	26	5.6	
3	male	22	4.2	
4	male	28	5.0	
5	male	20	5.0	
6	male	38	4.0	
7	female	33	4.2	
8	male	14	6.1	
9	male	26	6.6	
10	male	13	4.5	

From the above experimental data, we recognize that in both pyridoxine-deficient rats and rabbits H. duplex would live longer than in the controls.

Quantitative Analysis of Pyridoxine in Patients with Blepharoconjunctivitis Angularis

For the purpose of clinical experiment, a quantitative analysis of pyridoxine in the urine of patients was made, and the role of pyridoxine in patients with blepharoconjunctivitis angularis was examined. The experimental data, as shown in Table 7 came out with the following results: 4μg. to 6μg.% in the urine of normal persons (controls), while in patients the values were 1μg. to 2μg.% in five cases, 2μg. to 3μg.% in seven cases, and 3μg. to 4μg. % in six cases. This shows that pyridoxine quantity in the urine of patients with blepharoconjunctivitis angularis is, in general, less than in the controls. In addition to this fact, in only 3 out of 18 cases was H. duplex found.

Comment

Symptoms due to pyridoxine deficiency in man have not been known definitely, although there are many reports on symptoms in experimental animals. Accordingly, the symptoms in man have only been derived from the results obtained by administering pyridoxine to patients with clinical manifestations similar to those of pyridoxine-deficient animals. However, Mueller (1950) and Vilter (1953) made known the deficient symptoms by giving deoxypridoxine, known as antivitamin of pyridoxine. According to their reports, the symptoms in man are suppression of growth, microcytic hypochromic anemia, increase of xanthine in urine, disturbance of amino acid metabolism, and, as dermatic changes, seborrheic dermatitis around the eye, the nasolabial area, and the extremities. Also, symptoms of polyavitaminosis are seen: erosion around the mouth like cheilitis due to ariboflavinosis and glossitis and stomatitis angularis as seen in nicotinic acid deficiency.

In the experiments that Mueller did, two of eight cases showed, besides general symptoms, ocular manifestations similar to blepharoconjunctivitis angularis: congestion and scaling at the temporal angle. In the experiments Vilter made, 3 of 50 cases had conjunctivitis. It seems to be significant that our experiments in animals fed with mixed food came out with a result very similar to that of Mueller's and Vilter's experiment. In addition to this, reports have been made on the fact that the symptoms were not cured by administration of riboflavin or of nicotinic acid but by administration of pyridoxine.

Smith [13] also reported that cheilitis was cured by administration of pyridoxine. From the facts mentioned above, Mueller et al. thought that there might be some relationship between pyridoxine and riboflavin and nicotinic acid in their effects. Sato's riboflavin-deficient rabbits, Yamada's nicotinic acid-deficient rabbits, and also "Shibi-Gattchaki" disease, which is the typical phenomena widespread in the western part of Aomori Prefecture, though in some other parts of Japan, reported by Irinoda [14] as deficiency symptoms chiefly of riboflavin, nicotinic acid, and various other vitamins, all had blepharoconjunctivitis angularis. Bell

et al.[15] also reported that the amount of nicotinic acid in the urine of pyridoxine-deficient rats was less than that of the rats fed with pyridoxine. In addition to those facts, our experimental data that riboflavin and nicotinic acid in the urine and organs of pyridoxine-deficient animals showed only in small quantity as compared with the controls might mean that there is some relationship between pyridoxine and riboflavin and nicotinic acid.

Therefore, we believe that not only the clearly known fact that pyridoxine in vitro acts as a hydrogen acceptor but also the fact that in the living body it acts as one of the oxidation-reduction ferments holds true.

As for blepharoconjunctivitis angularis in the human, Morax[16] reported this for the first time in 1898. He found a certain bacteria in the secretion from a patient with blepharoconjunctivitis angularis and reported it as the cause of the disease. Since then, this disease has been known as one caused by H. duplex. However, a suspicion arose of this etiological cause. Yasuda,[17] examining 60 healthy persons, found the H. duplex in 43 persons. Mitsui and Hinokuma[18] found that 941 of 3008 outpatients had this bacillus, but only 195 cases had symptoms of blepharitis angularis. As for the pathological changes due to H. duplex inoculation, Morax reported that he noticed conjunctivitis four days after he dropped the cultured bacteria into the eye. Hoffman, Gifford, Erdmann, et al. reported the same results as Morax. As contrasted with this, however, Mitsui and Hinokuma[19] reported that cases positive for H. duplex showed no clinical symptoms; their experiments with human beings came out with the result that, of eight cases, five showed neither clinical symptoms nor bacterial findings and two showed only bacterial findings. Thus they concluded that the organism in the conjunctival sac does not necessarily account for the disease but that a certain condition would be furnished by it for falling ill. Hinokuma and Yamashita,[20] gave pyridoxine for this disease and cured five of eight cases without giving any other local therapy. They therefore emphasized that pyridoxine had a good deal to do with blepharoconjunctivitis angularis. Asahiuga and Goto[21] cured this disease by treating the patients with either unpurified pyridoxine or synthesized nicotinic acid. They, too, concluded that blepharoconjuntivitis angularis had something to do with riboflavin complex deficiency.

In order to study what pyridoxine deficiency has to do with blepharoconjunctivitis angularis we made some animal experiments. One of the pyridoxine-deficient rats suffered from a kind of conjunctivitis after 24 hours. H. duplex was found by culture at the 72d hour. In controls, however, neither clinical symptoms nor H. duplex was seen. In pyridoxine-deficient rabbits, two of five cases showed slight lacrimation, eye discharge, and congestion at the conjunctiva palpebrae at the 24th hour, and they were cured completely before the 48th hour, although the bacteria were seen until the 72d hour. In controls, however, only one of four cases was positive for the bacteria after cultured at the 24th hour. Thereafter, none were positive. From the experimental data the following may be concluded.

H. duplex has an affinity with conjunctiva palpebrae in pyridoxine-deficient condition, for, despite the fact that in pyridoxine-sufficient animals H. duplex inoculated into the conjunctiva can not live long, in pyridoxine-deficient animals the bacillus can live longer, as compared with the controls. From this fact we assume that pyridoxine deficiency makes it easy for H. duplex infection to occur and plays the chief role in developing blepharoconjunctivitis angularis. Therefore, H. duplex infection has no more than a secondary significance in blepharoconjunctivitis. In fact, the amount of pyridoxine in the urine of patients with blepharoconjunctivitis angularis is less than that of the controls, and only in 3 of 18 patients was the bacillus found. We believe, therefore, that the principal cause of bleph-

aroconjunctivitis angularis is pyridoxine deficiency.

Summary

By feeding rats and rabbits with pyridoxine (vitamin B_6)-deficient food, symptoms due to the deficiency and the following experimental results were obtained.

1. General symptoms due to pyridoxine deficiency.

(*a*) In almost all cases, the ears became congested and swollen; hair, stained, and growth was inhibited.

(*b*) In pyridoxine-deficient animals the amount of pyridoxine was markedly low as compared with the controls both in the urine of rabbits and in the organs of rats. In a pyridoxine loading test the deficient rabbits had a low excretion rate also.

(*c*) Both the quantity of riboflavin in the organs of pyridoxine-deficient rats and the quantity of riboflavin and nicotinic acid in the urine of the deficient rabbits tended to be decreased as compared with the controls.

2. Changes in the visual organ due to pyridoxine deficiency.

(*a*) Clinically noticed are blepharitis angularis, blepharitis marginalis, conjunctivitis palpebrae, and corneal vascularization.

(*b*) The histopathologic pictures are (1) hyperkeratosis at the eyelid margin and skin, vascular dilation in the subcutaneous tissue, and edema of the tissue. Some of the cases showed blepharitis and a diffuse infiltration of lymphocytes, plasma cells, and neutrophil leukocytes in both cutaneous and subcutaneous tissues of the eyelid. In the conjunctiva palpebrae an infiltration of lymphocytes, monocytes, and plasma cells to the layer right below the epidermis was seen. (2) In some cases at the cornea were seen dilated vessels around the limbus, infiltration of lymphocytes around the vessels, and scattered neutrophil leukocytes. A neovascularization also was seen at the upper layer in the substantia propria.

3. Significant relation between blepharoconjunctivitis angularis and pyridoxine deficiency.

(*a*) Hemophilus duplex (Morax-Axenfeld bacillus) inoculated into pyridoxine-deficient animals survived longer than those inoculated into the controls (pyridoxine-sufficient animals).

(*b*) Patients with blepharoconjunctivitis angularis had less pyridoxine in urine as compared with the controls.

From all these findings it may be concluded that blepharoconjunctivitis angularis is caused chiefly by pyridoxine deficiency and that H. duplex infection has only a secondary significance in this disease.

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Cultivation of Adult Human Iris in Vitro

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The clinical observation that the iris does not show any evidence of regeneration of its tissue elements following aseptic iridectomy has never been satisfactorily explained.

Up to date there have been very few studies on the healing process of the human iris and only little experimental work on this subject in animals. Daniel (1944) studied the healing process following experimental iridectomy in rabbits and concluded that the iris did not show any tendency to bridge the surgical coloboma with permanent fibrous scar tissue.

To investigate this unusual lack of proliferation of the cells of the iris following injury, tissue culture studies of the human iris were undertaken. While embryonic and adult irises of different vertebrates have often been explanted and kept as permanent strains, adult human iris has to our knowledge never been cultivated successfully.

Material and Methods

Thirty-two segments of human iris were obtained from various surgical procedures, taken into sterile test tubes containing 2 ml. of isotonic saline, kept at 4 C and explanted within one to two hours. The larger specimens were divided into two or three pieces before explantation. The cultures were grown either in D-3.5 Carrel flasks or by the Maximow method as lying drops. The Carrel flasks contained a solid phase, consisting of 0.5 ml. of chicken plasma, 1 ml. of Earl's saline, and 3 drops of diluted chick embryo extract, and a fluid phase, consisting of 1 ml. of Earl's nutrient (40% Earl's saline, 40% horse serum, and 20% chick embryo extract). The medium in Maximow slides consisted of a drop of chicken plasma and a drop of 50% chick embryonic extract. A drop of Earl's nutrient was placed on the surface of the clot.

The cultures were kept at 37 C for a period of six to eight weeks. Every third day they were washed and fed with Earl's nutrient. The pH of the nutrient fluid was adjusted to 7.4 to 7.6. In some of the cultures an alkaline medium with pH ranging from 8.5 to 9.0 was employed. At intervals fresh plasma was used for patching to counteract occasional liquefaction of the clot.

In some of the cultures human serum was added to the solid phase making a final concentration of 10%. This batch of cultures was regularly fed with a modified Earl's nutrient which contained human serum instead of horse serum.

After varying periods of time some of the cultures were fixed either in Carnoy's solution or in 4% formalin for histological examination.

Observations

Out of 22 specimens taken from patients with cataract, 14 (64%) showed good growth, 2 showed poor outgrowth, and 6 (27%) did not grow at all. Two irises from patients with wide-angle glaucoma and one prolapsed iris exhibited active proliferation, while four specimens of iris from cases of primary narrow-angle glaucoma, two irises from patients with secondary glaucoma, and one atrophic iris did not show any growth at all. The patients'

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ages, which ranged from 9 to 84 years, did not influence the outcome of the tissue culture.

The first cells, as a rule, migrated from the explanted iris at about the 5th or the 6th day of incubation and occasionally as late as the 11th day. In most of the cultures, migration of cells was preceded by the outgrowth of fibrillar processes of different diameters.

The first cells to start active proliferation were the muscle cells, both pigmented and nonpigmented. These were followed by fibroblasts and endothelial cells. The neuroepithelial cells and nerve cells were the last to appear. Owing to the relatively long latent period (i. e., the lapse of time between explantation and the first evidence of growth) and the subsequent slow rate of proliferation, the area of outgrowth was relatively small during the first two weeks of cultivation but gained in size later on.

Smooth Muscle Cells.—Both the pigmented dilatator and the unpigmented sphincter muscle cells grew readily in the culture medium containing Earl's saline adjusted to pH 7.4 to 7.6. These muscle cells grew less vigorously in the alkaline medium (pH 8.5 to 9.0).

Fig. 1.—Dilator pupillae muscle cells. The small amount of pigment granules makes it possible to see how single cells adhere to each other to form thicker fibers; × 280. All figures except Figure 9 were photographed from living cultures in Carrel flasks with the aid of Leitz' Panphot.

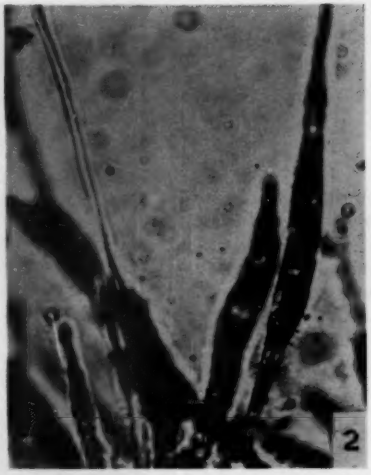


Fig. 2.—Same muscle cells as in Figure 1. The abundant pigmentation obscures the cell boundaries. The partly covered nuclei can be seen as clear irregular dots in the fibers; × 280.

The dilatator muscle cells contained varying amounts of pigment (Figs. 1 and 2). The broader plump part of the spindle-shaped cell adhered to the fusiform fibrillar end of a neighboring cell, thus giving rise to a thicker muscle fiber. Sometimes single muscle cells were connected with each other by their fusiform endings, forming long and slender cell chains.

The unpigmented highly refractile sphincter muscle cells grew either in long slender chains (Fig. 3) or adhered laterally to form a broad network of anastomosing bands (Fig. 4). They showed a marked gliding migratory tendency, so that single cells or small groups of cells could be found at a considerable distance from the original explant. These cells often grew in a bent, semicircular manner, owing to the tension of their fibrils (Fig. 5).

Fibroblasts.—In most cultures the fibroblasts grew abundantly, dominating all the other cellular elements. In other cultures they intermingled with smooth muscle cells. The fibroblasts usually formed an irregular dense reticulum, but sometimes a circular

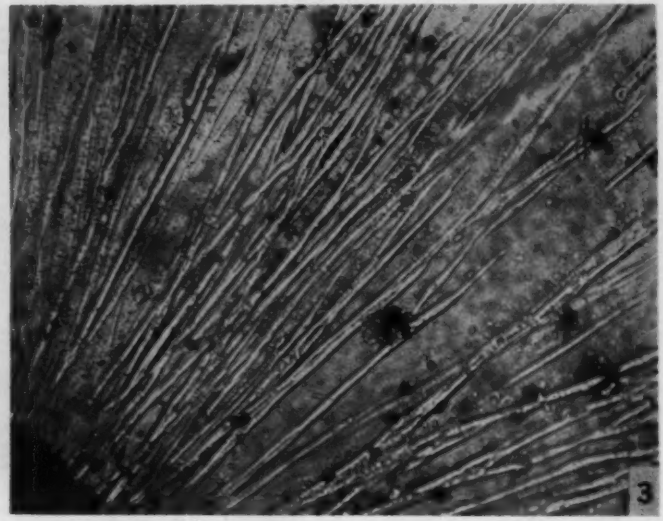


Fig. 3.—Highly refractive sphincter pupillae muscle cells, 26 days in culture; × 150.

or stratified pattern was observed (Fig. 6). They grew as well at a pH 7.4 to 7.6, as in the more alkaline medium (pH 8.5 to 9).

Endothelium.—In some cultures a rich growth of endothelium occurred. It appeared as a thin flat lace-like membrane with large interspaces between the cell groups. Intercellular spaces were seen between the single cells.

The cell bodies were usually flat and pale but sometimes elongated and slender (Fig. 7). Numerous mitotic divisions were observed, the course of which could be easily followed, owing to the thinness of the membrane.

The mitotic process was different from that of dividing fibroblasts. No pseudopodial activity (blebbing) of the cytoplasm signaled the beginning of the telophase, and no constriction in the equatorial plane occurred. After a relatively long metaphase of about 15 minutes and a short ana- and telophase, the dividing cell fell apart rapidly. A wide cleft, without any connecting protoplasmic

Fig. 4.—Same muscle cells forming a network of broad, anastomosing bands, 19 days in culture; × 100.

Fig. 5.—A group of cells of the same muscle. Having migrated to some distance from the original explant, they still show a tendency to bend in a semicircular fashion. Forty-seven days in culture; × 150.

bridge, separated the two bell-like daughter cells (Fig. 8).

One of the cultures with a rich endothelial growth showed, after fixation and sectioning, a layer of flat endothelial-like cells on the anterior surface of the explanted iris (Fig. 9).

Neuroepithelium.—The first signs of epithelial growth usually occurred after the fibroblasts, muscle cells, and endothelial cells showed abundant proliferation. After the late start further growth was steady, and ultimately extensive epithelial membranes were formed. When growing on the surface of the culture clot, small islets of polygonal pigmented and unpigmented cells were observed (Fig. 10).

The epithelium of the iris grew better in the more alkaline medium.

Nerve Cells.—Fine filamentous neurofibrils might appear as soon as three days after explantation. The corresponding cell bodies migrated clear out of the explant

Fig. 6. — Fibroblasts growing in a striated pattern, 32 days in culture; × 150.

Fig. 7.—Lace-like endothelial membrane with delicate flattened cells in the same culture as shown in Figure 6; × 140.

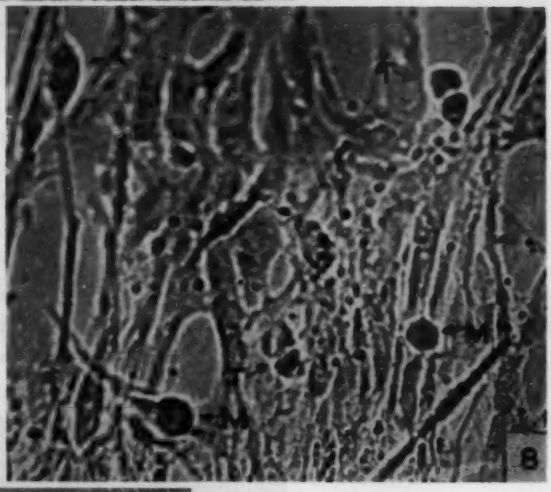


Fig. 8.—Endothelial membranes with several cells in mitotic division. Note at *T* (telophase) the sister cells showing a wide, clear cleft after an abrupt division. *M*, metaphase; *A*, anaphase; × 200.

Fig. 9.—Section through the explant of the same culture as in Figure 8, fixed in Carnoy's fluid and stained with hemalum-eosin after 42 days of cultivation in vitro. A layer of flat endothelial cells can be seen on the anterior surface of the iris. Note the well-preserved structure of the explant; × 140.

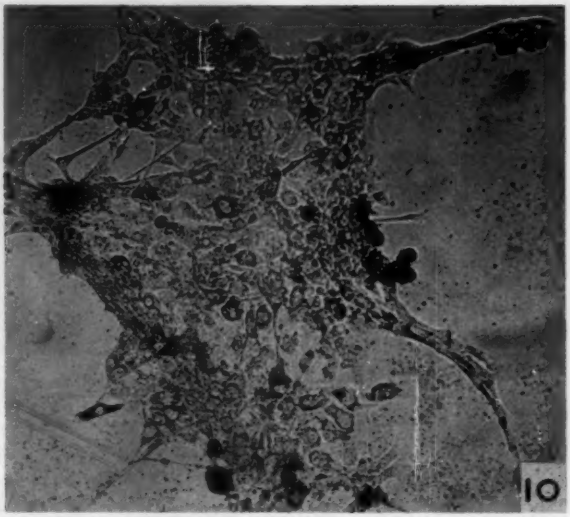


Fig. 10.—An isolated islet of epithelial cells growing on the surface of the culture clot, 28 days in culture; × 100.

about eight days later. The cells were small, pyriform and sometimes stellate. Their cytoplasm was smooth; their nucleus, clear, poor in chromatin, and with a fairly big nucleolus. Their fibrils were fine, with varicose swellings, and formed an anastomosing network (Fig. 11). Mitotic divisions of these cells were sometimes observed in the cultures. The mitosis proceeded in a similar way as described above for endothelial cells of the iris, except that a bridge of protoplasm was seen after the cleavage between the two daughter cells. The terminal axon-like process either persisted during the whole mitotic process or became thicker and shortened.

Chromatophores.—The typical branched chromatophores were rarely seen in the cultures (Fig. 12). They usually appeared in a contracted rounded form (Fig. 13). The nuclei were not obscured by the pigment granules.

Comment

In this study of the behavior of the adult human iris in tissue culture the small size of the specimens as well as the delicate texture of the tissue presented some technical difficulties.

An important factor in the successful growth of the culture was the condition of the iris tissue. While the irises from cata-

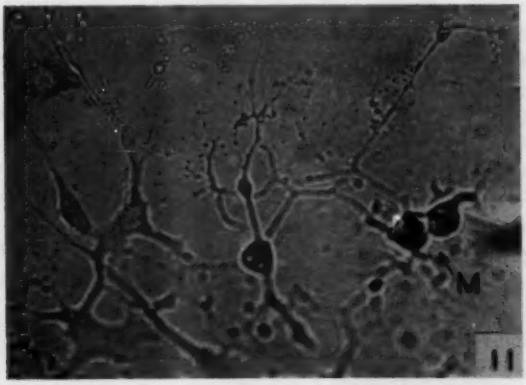
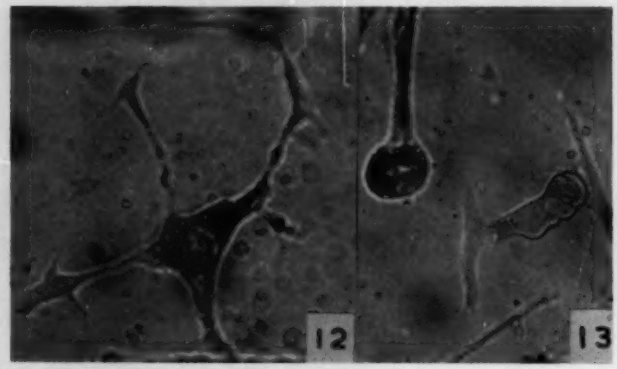


Fig. 11.—A group of nerve cells with an anastomosing, angular network of neurofibrils with varicose thickenings. Note the dark cell in division at *M*, showing thin connecting bridges between the daughter cells and a thick shortened dendrite on one of the daughter cells. A group of pale stellate nerve cells with branched processes can be seen on the left. Twenty days of cultivation; × 150.



Figs. 12 and 13.—Two melanophores, one being in an expanded and the other in a contracted state. The nuclei are only partly covered by pigment granules; × 450.

ract cases showed a high percentage of good growth, no growth whatsoever was obtained from the irises of patients with primary narrow-angle glaucoma who had suffered from repeated attacks of increased intraocular pressure. The one specimen of iris which was markedly atrophic did not proliferate.

The rate of growth remained slow in all the media tried in spite of the continuous use of a growth-stimulating supernatant.

Histological preparations of the central pieces of the original explants which had been kept in culture for several weeks showed a well-preserved structure.

The presence of an endothelial layer in the anterior surface of the human iris is still disputed, though most authors (Wolff, 1940; Duke-Elder, 1942) affirm its existence. Our findings indicate its presence. This kind of growth must be distinguished from the growth of vascular endothelium. According to White (1954), the vascular endothelium retains the property of forming new capillary tubes in vitro. The endothelium obtained in the present study formed extensive thin membranes of very delicate cells, and the formation of endothelial tubes was not observed. Duke-Elder (1942) and others believe that the iris endothelium is a continuation of the corneal endothelium. Cell formations similar to those of the endothelial elements in our cultures were described in cultures of corneal endothelium (Poleff, 1928). This finding also supports the view that the endothelium obtained in cultures of the adult human iris was true iris endothelium.

Summary

Adult human iris obtained at operation was grown in tissue culture.

The latent period of the outgrowth of cells was very long, and the rate of growth was slow.

All the different cellular elements of the iris, except for blood vessels, proliferated in these cultures. The presence of an iris endothelium was confirmed.

The original structure of the explants was preserved for long periods in those cases where growth was obtained.

Irises taken from cataract cases grew more readily than the ones obtained from patients suffering from primary narrow-angle glaucoma.

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Use of Piromen in Ophthalmology

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Piromen is a pyrogenic substance obtained from Pseudomonas aeruginosa. This material has been shown to be a relatively nontoxic and a nonanaphylactogenic bacterial substance.[1,2] Nesset and his associates[3] have shown that it is nonprotein in nature. A number of investigators have shown that pyrogens are polysaccharides. They have been termed polysaccharides primarily because reducing sugars are obtained on hydrolysis. The nature of all the component reducing sugars is not as yet well known, but hexosamine has been fairly constantly detected. Hexosamine appears to be the only reducing sugar essential for fever production, according to these authors.

Since it has long been known that artificial fever has therapeutic value, research groups immediately started experimenting with Piromen for the artificial production of fever. It soon became evident to some of the research men working with this substance that relatively small doses which were not followed by any marked constitutional symptoms gave fairly good results. The intravenous administration of Piromen is characterized by marked mobilization of the reticuloendothelial system, by transient leukopenia and eosinopenia followed by neutrophilic leukocytosis, by lymphoid tissue hyperplasia, and by a stimulatory action on the adrenal cortex. Marked elevation of the body temperature occurs only when Piromen is given in doses larger than will be recommended in this article. As in foreign-protein therapy in general, the beneficial therapeutic effects of Piromen are probably not due to any particular one of these reactions but rather to a combination of these. According to Lonsen and Liebert,[4] microscopic examination of the organs of animals killed after they had been subjected to long and massive administrations of Piromen did not show any signs of permanent damage. These authors concluded that this material effects a mobilization of the general body defenses within a wide range of safety. It appeared to them that Piromen in large doses seemed to be safer than malaria or typhoid vaccine therapy in persons over 60 years of age.

Examination of the suprarenal glands of rabbits that had received recent administrations of Piromen, in the experiments of Windle and his co-workers,[5] showed changes which were suggestive of an acceleration of cortical secretory activity.

The administration of Piromen does not impose the severe restrictions on the patient that the intravenous administration of typhoid vaccine does. The symptoms produced by this material are not markedly incapacitating in the average case. The treatments can be administered on an ambulatory basis. For best results the preparation should be administered intravenously. The intravenous administration of Piromen is usually followed in 45 minutes to an hour by a chill. A slight headache is also part of the ordinary reaction. The patients may also complain of a certain amount of myalgia and, rarely, of nausea. Most of these symptoms are easily relieved by acetylsalicylic acid, the use of which does not appear to interfere with the beneficial effects of Piromen.

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From Department of Ophthalmology, School of Medicine, University of Puerto Rico.

The initial dose of Piromen for the treatment of eye diseases should be 5μg. Two days later the dose is increased to 7.5μg. Subsequent administrations should consist of 10μg. of the material every two days until the treatment is completed. The number of treatments depends on the individual case and on accurate observations at regular intervals. I have used Piromen in the treatment of about 200 cases of assorted eye diseases. These have included such varied conditions as traumatic iritis, postoperative iridocyclitis, acute chorioretinitis, acute nongranulomatous uveitis, chronic nongranulomatous uveitis, central retinitis, vitreous opacities of undetermined origin, retrobulbar neuritis, alcohol amblyopia, optic neuritis, vitreous hemorrhage, disciform keratitis, and keratitis. In a great majority of these cases either a cure was obtained or the improvement was of such degree that it did not leave any doubts in my mind that Piromen is a substance of decided therapeutic value in the treatment of ophthalmic diseases.

Although it may sound farfetched to be talking about a new pyrogenic agent at a time when the reputation of corticotropin and the corticosteroids is so solidly established in ophthalmology, I believe that there are still indications for these substances. We all know from experience that there are conditions in which steroids will not work and in which fever therapy or pyrogens will. There are also conditions in which the prolonged use of any of the steroid preparations may be considered risky for a given patient. In cases like these the use of a pyrogen such as Piromen may be a more-indicated method of treatment.

TABLE 1.—*Leukocytic Response to Five Micrograms of Piromen in a Case of Keratitis*

Hour	WBC	Polymorphonuclear Cells	Lymphocytes	Monocytes	Eosinophils
8:00 a. m. *	5,100	52	43	0	5
10:00 a. m.	13,800	86	12	0	2
12:00	8,300	77	23	0	0
2:00 p. m.	6,750	70	26	0	4
4:00 p. m.	6,950	54	29	0	6

* Piromen was administered immediately after the blood sample for the 8:00 a. m. count was taken.

TABLE 2.—*Leukocytic Response to Five Micrograms of Piromen in a Case of Postoperative Iridocyclitis*

Hour	WBC	Polymorphonuclear Cells	Lymphocytes	Monocytes	Eosinophils
8:00 a. m. *	9,000	60	33	4	3
10:00 a. m.	9,600	83	17	0	0
2:00 p. m.	14,500	95	5	0	0
4:00 p. m.	21,750	95	5	0	0

* Piromen was administered immediately after the blood sample for the 8:00 a. m. count was taken.

Tables 1 and 2 show that the peak of the total and polymorphonuclear leukocytosis following the administration of Piromen is variable in its occurrence, in some cases occurring two hours after administration (Table 1) and in others occurring as late as eight hours after administration (Table 2). The total leukocyte count attains a height of two and one-half to three times the initial count. The blood picture is usually restored to normal in 16 to 24 hours after Piromen administration.

Tables 1 and 2 show typical responses to Piromen administration in two patients treated by me. This response is similar to that following stress and the systemic administration of cortisone and adrenocorticotropic hormone. It is therefore likely that, in addition to the leukocytosis, the production of cortisone is an important action of Piromen.

It is also suspected that Piromen brings about or produces an increase in the number of circulating antibodies in much the same way that typhoid vaccine does.

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Composite Mounting of Thirty-Five-Millimeter Color Transparencies

ARTHUR SMIALOWSKI and SIGMUND VAILE, M.D., Toronto, Canada

The purpose of a composite mounted slide is to show more than one view at the same time, with use of one projector. By this method portions of transparencies of related subjects are mounted together on one slide.

A great variety of mounting combinations and arrangements are possible. They will largely depend on the subject matter and need.

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St. Michael's Hospital, Photography Department.

There are some considerations to make before taking the photographs, such as choice of field, i. e., horizontal or vertical; relationship of subject size, and similarity of lighting arrangement and of background color.

Procedures in Making the Composite Slide

Selection and planning before cutting each individual transparency is necessary. It is important that the cut be straight.

Fig. 1.—The two transparencies are cut to size and are positioned in the mask.

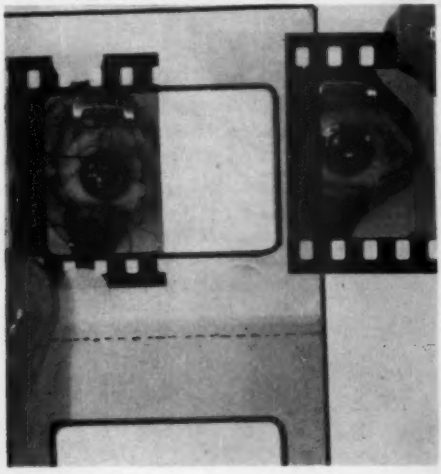
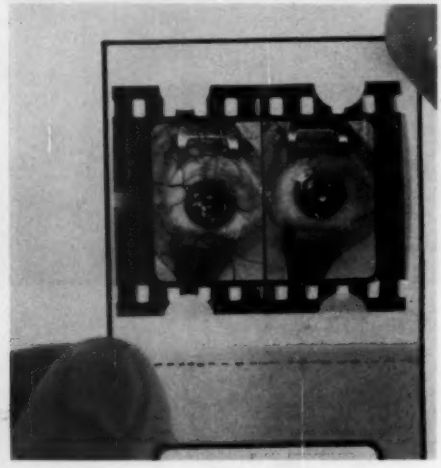


Fig. 2.—The transparencies are overlapped about 1 mm.



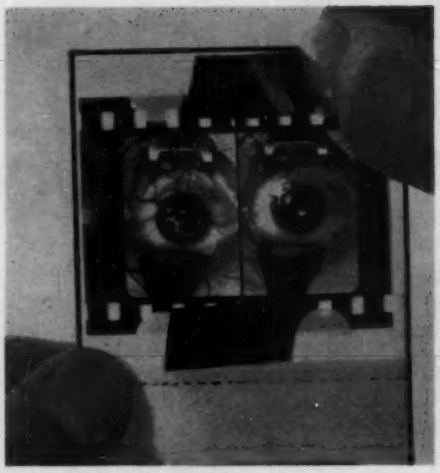


Fig. 3.—Tape is applied to outside edges only.

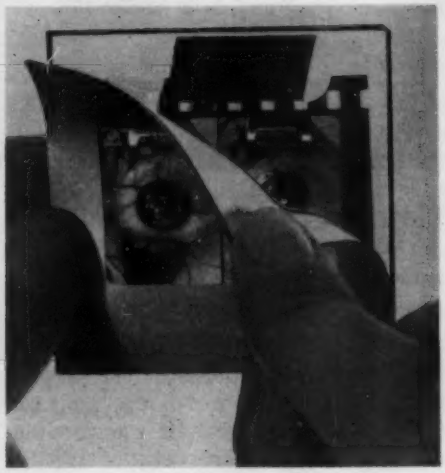
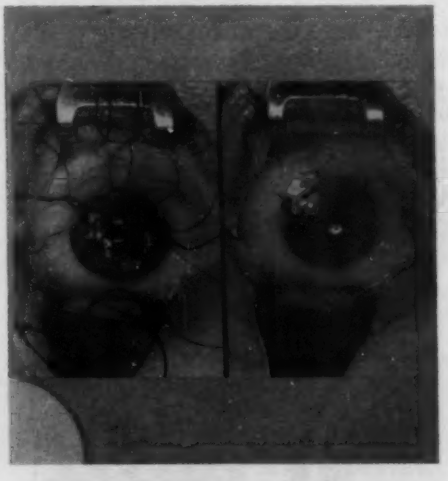


Fig. 4.—The mask is folded together.

Fig. 5.—The final appearance of the mounted slide.



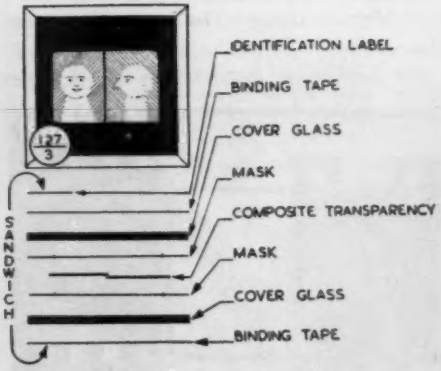


Fig. 6.—Diagram of the assembly.

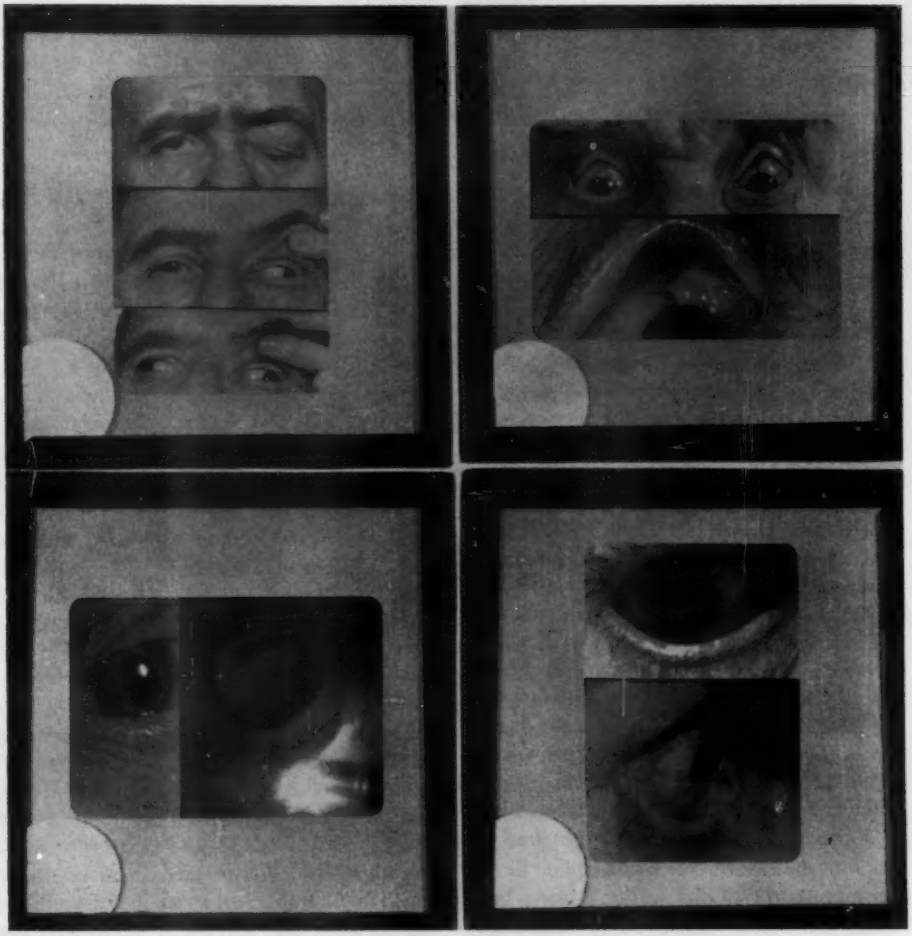


Fig. 7.—A few sample transparencies mounted by this technique.

After two or more transparencies are cut to appropriate size they are arranged in the mask so that they overlap each other 1 mm. This gives a very nice effect and is a far better method than trying to join them together with tape or glue. The outside edges of the components are held down by strips of tape.

The steps are clearly illustrated by the accompanying photographs.

St. Michael's Hospital, 30 Bond St.

Annual Reviews

Ophthalmic Pharmacology and Toxicology

W. MORTON GRANT, M.D., Boston

This review of ophthalmic pharmacology and toxicology covers the period April, 1957, to March, 1958.* It is arranged in a manner similar to the reviews of the same subject in the past two years.[65,66] Ophthalmic pharmacology comes first, with the following headings: Influence of Drugs on the Intraocular Pressure, Mydriatic-Cycloplegic Drugs, Corticosteroids and Other Anti-Inflammatory Agents, Influence of Drugs on Retinal and Uveal Vessels, Chemotherapeutic and Antibiotic Substances, Pre- and Postoperative Medications, Pharmacologic Influences on the Cornea, and Miscellaneous. Ophthalmic toxicology follows, with the following headings: Cornea and Conjunctiva, Lens, Iris and Pupil, Retina and Optic Nerve, and Miscellaneous. Occasionally it is difficult to be sure whether an observation belongs under the heading of pharmacology or toxicology. An example is the effect of drugs on the electroretinogram and on flicker perception; these observations have been rather arbitrarily consigned to toxicology, because they deal in part with hallucinogenic drugs and with effects not ordinarily utilized therapeutically in ophthalmology.

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Howe Laboratory of Ophthalmology, Harvard Medical School and Massachusetts Eye and Ear Infirmary.

* The journals surveyed included *Acta ophth., Acta pharmacol. et toxicol., Acta physiol. scandinav., Am. J. Ophth., Am. J. Physiol.,* A. M. A. ARCH. OPHTH., *A. M. A. Arch. Indust. Health., Ann ocul, Brit. J. Indust. Med., Brit. J. Ophth., Bull. Soc. belge opht., Chem. Abstr., Docum. ophth., J. A. M. A., J. Gen. Physiol., J. Pharmacol. & Exper. Therap., Klin. Monatsbl. Augenh., New England J. Med., Ophth. Lit., Ophthalmologica, Pharmacol. Rev., Proc. Soc. Exper. Biol. & Med., Survey Ophth., Tr. Am. Acad. Ophth., Tr. Am. Ophth. Soc., von Graefes Arch. Ophth., and Zentralbl. ges. Ophth.*

Ophthalmic Pharmacology

Influence of Drugs on the Intraocular Pressure.—For the fourth year since the introduction of acetazolamide (Diamox) into ophthalmology, this drug has maintained an important position in the treatment of glaucoma, and it has continued to intrigue both laboratory and clinical investigators. The clinical usefulness of acetazolamide in relief of acute angle-closure glaucoma as well as in control of certain cases of chronic glaucoma has become well established. However, it has been necessary again to call attention to the undesirable consequences of attempting to maintain control of angle-closure glaucoma by continuing administration of acetazolamide in place of operation.[19,30] In angle-closure glaucoma the initial reduction of intraocular pressure, which may be obtained by means of acetazolamide, provides favorable conditions for performance of iridectomy or other operation; however, if, owing to a false sense of security when the intraocular pressure has been lowered by acetazolamide, operation is not performed, synechiae in the angle of the anterior chamber may become more firmly established, and in the course of time treatment may become much more difficult both medically and surgically.

Laboratory investigation of the action of acetazolamide has continued mainly along the lines of analysis of the influence of this drug on the composition of the aqueous humor and on the relative rates of accumulation of test substances in the anterior and

posterior chambers. A comprehensive survey of the present knowledge of chemical composition of aqueous humor in human, monkey, and rabbit eyes by Becker substantiates the fact that human and monkey have an excess of chloride and a deficiency of carbon dioxide in the aqueous humor compared with the plasma, while the rabbit aqueous humor has excess bicarbonate and is deficient in chloride.[21] Furthermore, in the primates, the pH of aqueous humor is lower than in the plasma, whereas in rabbits the pH is higher. Despite these differences, all respond to the administration of acetazolamide with a decrease in rate of flow of aqueous humor, and this is associated with a shift in the concentrations of chloride, bicarbonate, and hydrogen ions so that the differences between concentration in aqueous humor and plasma are decreased. The concentration of ascorbate, on the other hand, appears to be a special case, in that its concentration is increased in the aqueous humor in each species following administration of acetazolamide.[21] Further information on the relationship of ascorbate to formation of aqueous humor and action of acetazolamide was obtained by studies on the guinea pig, which can readily be made scorbutic. The aqueous composition of the guinea pig is similar to that of the rabbit, and the effect of administering acetazolamide has similar influence on intraocular pressure and bicarbonate levels in the aqueous humor of guinea pigs and rabbits. The level of ascorbate appeared to have no influence on bicarbonate of the aqueous, rate of flow, intraocular pressure, or action of acetazolamide, since these factors were all found to be the same in scorbutic animals as in normal ones.[20] Protein and several of the amino acids which are normally present in plasma and aqueous humor have been found to increase in concentration in the aqueous humor under the influence of acetazolamide, but probably not to the extent that ascorbate increases.[7,59] An attempted study of the effect of acetazolamide in dogs indicates that there is a decrease of sodium and carbon dioxide content and lowering of pH in the aqueous, but this information is not of much significance without information on the plasma concentrations in the same animals.[155] Further studies have been made on the time course of changes in aqueous composition relative to administration of acetazolamide. Earlier studies have shown that in rabbits a decrease in pH and bicarbonate concentration occurs promptly in the posterior chamber but that the change in composition of the aqueous humor in the anterior chamber becomes evident only gradually over the course of an hour. During this time, and especially over longer periods of time, the possibility exists not only that the composition of the aqueous humor may be influenced by a direct action of acetazolamide on the eye but also that there may be a reflection of systemic acidosis and other changes in plasma composition. In recent attempts to hold the plasma bicarbonate and pH constant after administration of acetazolamide to rabbits, this was accomplished at least for the first three hours, and during this time the bicarbonate and pH of both posterior and anterior chamber aqueous humor decreased under the influence of systemically administered acetazolamide.[68]

The sodium and potassium concentrations of the aqueous humor do not appear to be altered significantly relative to the plasma concentration under the influence of acetazolamide, despite shifts in anion composition of the aqueous humor.[53,72] In rabbits the concentration of potassium does decrease slightly more in the serum than in the aqueous humor; however, on an osmotic basis the difference is slight.[72] It may be noted that failure to detect a change in the concentration of sodium relative to water or of water relative to sodium under the influence of a drug such as acetazolamide does not establish that the rates of transfer of these substances into the eye are unaltered, since the same finding would be obtained if the rates of both were decreased or increased to equal degrees. On the other hand, attempts have been made to detect an influence of acetazolamide on the rate of

movement of sodium into the aqueous humor by measurement of the rate of change of concentration of radioactive sodium in the blood and in the aqueous humor following intravenous injection in animals, but no drug-induced alteration has been detected in this way.[40,73] Similar experiments have been carried out with use of heavy water, but no significant influence on the rate of concentration change in blood and aqueous humor has been detected following administration of acetazolamide.[73] These negative findings from tracer studies constitute an enigma and suggest that further analysis of the data is needed. In particular, it may be helpful to translate rate of change of concentration into terms of absolute amounts of substance transferred into the eye per unit time. Other evidence, such as the considerable increase in ascorbate concentration in the aqueous humor under the influence of acetazolamide, the decrease in total flow of aqueous humor demonstrated by means of tonography and fluorescein-appearance time, and the fact that no definite alteration of osmotic pressure of the aqueous humor has been demonstrated following administration of acetazolamide, all suggest that there should be a proportionate decrease in the absolute rate of transfer of substances such as sodium and water into the eye.

Although the precise mechanism by which acetazolamide partially suppresses the formation of aqueous humor has not yet been established, the best working hypothesis continues to be that the drug exerts its effect primarily by inhibition of carbonic anhydrase in the eye, and not by way of some systemic action. Considerable difficulties are encountered in precise localization and demonstration of carbonic anhydrase in ocular tissues, and precise localization of the effect of the drug awaits further technical developments.[28] Despite universal failure to obtain a pressure-lowering action by injecting acetazolamide subconjunctivally or by applying it to the eye as drops, sound evidence of a local ocular effect has been obtained when it has been applied via the circulation to the eye. Intracarotid infusion in cats causes a greater and more rapid fall of intraocular pressure on the side of the infusion than in the eye on the other side.[158]

In studies of the hydrodynamics of human eyes by means of tonography, an earlier report that acetazolamide decreases the facility of outflow has been substantiated.[87,153] This decrease in the facility of intraocular pressure, tending to maintain it at its initial level despite partial suppression outflow has a homeostatic influence on the of aqueous inflow by acetazolamide. Interestingly, this homeostatic influence has been found to be considerably more efficient in normal eyes than in eyes having open-angle glaucoma. The fact that acetazolamide more often succeeds in lowering the intraocular pressure in glaucomatous eyes than in normal eyes has been explained on this basis.[87,153] Comparative studies of the influence of the intraocular pressure itself upon facility of outflow have been carried out by perfusion of enucleated pig eyes, and it has been determined that decreasing the rate of flow and the intraocular pressure under these conditions causes an increase in facility of outflow, rather than the decrease which is observed in vivo in normal eyes of human beings and rabbits when the rate of flow is lowered by acetazolamide.[153] The mechanism for the effect on facility of outflow remains to be elucidated.

Clinical investigations concerning acetazolamide have of late been concerned principally with testing and comparing other carbonic anhydrase inhibitors, with the aim of finding substances which may have a more favorable ratio of pressure-lowering action compared to undesirable side-effects. Rarely have any dangerous side-effects of acetazolamide been noted,[66] but fairly commonly anorexia, malaise, and paresthesias have limited the usefulness of the drug in control of chronic glaucoma. It is desirable to find substances having a more selective effect on the eye with fewer systemic manifestations if possible. So far, no other carbonic anhydrase inhibitor has been demonstrated clinically to have any great superiority. Dichlorphenamide has been found in animals

to have effects similar to those of acetazolamide, and in patients it has also been found to have a similar pressure-lowering action. A smaller dose of dichlorphenamide is required for these effects, but no consistent advantage in respect to side-effects has been demonstrated, although in occasional patients this new drug has seemed to have some advantage.[22,72] Chlorothiazid has been disappointing with respect to treatment of glaucoma, in that it does not significantly lower the intraocular pressure when administered in tolerable doses.[22,72] Neptazane appears at present to be the most promising substitute for acetazolamide, exhibiting less-troublesome side-effects than the latter in numerous cases.[22] A carbonic anhydrase inhibitor known as Squibb-MC-9367 has been reported to be comparable to acetazolamide in influence on the intraocular pressure, but this drug has been tested only in single doses, and the manufacturer has recommended against its use over a prolonged period because of systemic toxic effects.[16] Ethoxzolamide (Cardrase), another sulfonamide compound having strong carbonic anhydrase inhibiting effect, has also been shown to be effective in lowering the tension of glaucoma, and there is some indication that a dosage of approximately half that of acetazolamide may be used.[22,109] However, no clear indication has been given in preliminary studies comparing this new drug with acetazolamide in glaucomatous patients that the ratio between antiglaucoma effect and unwanted side-effects is consistently different from that of acetazolamide. The side-effects apparently are similar. A somewhat misleading impression may be given by advertisements stating that a drug such as this has "twice the potency" of previously available agents, since the important thing is not whether a smaller dose can be used but whether a greater effect in lowering intraocular pressure can be achieved at a dosage the patients can tolerate without excessive side-effects. What would be most advantageous would be a drug which could be used with regular success in patients who do not tolerate acetazolamide.

Several studies have been made in the past year on the effects of systemically administered drugs other than carbonic anhydrase inhibitors upon the intraocular pressure. The pressure-lowering effects of intravenously administered dextrose, sucrose, and urea have been compared in monkeys. However, the dosage of urea which was tested provided approximately six times as many osmotically active molecules as did the dose of sucrose, and it is not surprising under these conditions that a considerably greater fall in intraocular pressure was obtained with urea. The lowering of pressure lasted for about three hours, and in the case of urea it was accompanied by no other notable toxic effect than a transient hemoglobinuria; the suggestion was put forth that urea might be tried in the treatment of glaucoma in human beings.[27]

Further observations have been reported on the effects of oral administration of the ganglion-blocking agent pentolinium bitartrate (Ansolysen), which was mentioned in last year's review.[66] It had been reported that in normal human eyes a slight fall of intraocular pressure follows parenteral administration of this drug, despite an accompanying impairment of facility of outflow found by tonography; it has been deduced that formation of aqueous humor must be partially suppressed in some manner. More recently, in patients with open-angle glaucoma, oral administration of 20 mg. of the same drug was found to cause only an approximate 6% decrease in intraocular pressure, accompanied by a small fall in blood pressure.[118] On the other hand, in these same patients after the intraocular pressure was lowered by means of pilocarpine, pentolinium bitartrate exhibited an effect more closely resembling that in normal eyes, causing an approximate 12% further decrease in the pressure along with some impairment of facility of outflow.[118] It seems that considerably more studies of these complex relationships and further analysis of factors influencing the validity of tonographic estimation of facility and rate of

aqueous outflow are needed before these effects can be completely understood.

Further observations were made on the influence of the tranquilizing drugs, such as Rauwolfia serpentina, chlorpromazine, and phenobarbital, on the intraocular pressure. As mentioned in last year's review, Rauwolfia serpentina was found to have no influence on the intraocular pressure in rabbits. Now its effect in human beings has been studied at some length, and the results have been analyzed statistically.[79] Intravenous injection of single doses of 35μg. to 155μg. per kilogram gave a decrease averaging 5.3 mm. in normal eyes and 30.2 mm. in glaucomatous eyes, with wide individual variations. In general the decrease in pressure appeared slowly, being first detectible at about 1.8 hours, with a maximum effect at 8.7 hours and a tendency to return toward base line at 23.9 hours. At least the early part of this effect upon the intraocular pressure appeared to be associated with change in the arterial blood pressure, and it was found that both changes could be prevented by infusion of arterenol intravenously. Furthermore, repeated intravenous doses of reserpine did not prevent the tension from returning to its original value. With daily oral treatment with the drug for periods longer than eight weeks generally no influence on intraocular pressure in normal human eyes was obtained, but in patients having glaucoma the mean intraocular pressure was commonly found to be about 2 to 4 mm. lower under the influence of the drug than during a period of placebo administration. Little attempt was made to correlate differences in results with different kinds of glaucoma.[79] The pressure-lowering effect of systemically administered chlorpromazine in acute glaucoma has again been noted, and also "in simple glaucoma" a fall in pressure lasting several hours has been described.[34] Phenobarbital is reported to cause some decrease in pressure in both normal and glaucomatous eyes, whereas an excitatory drug, methamphetamine, injected subcutaneously is said to cause some rise in pressure. These effects have been interpreted as involving diencephalic control of intraocular pressure.[34]

A decrease in intraocular pressure in rabbits was found to follow the injection of a muscle relaxant, mephenesin (3-*o*-toloxy-1,2-propanediol; Myanesin), reaching a maximum in 5 to 135 minutes and often lasting for several hours. The mechanism for this effect has not been established, but it does not appear to be attributable either to a fall in blood pressure or to relaxation of the extraocular muscles, for both of these effects were of considerably shorter duration.[88] Anthranilic acid and certain of its derivatives administered orally are reported from Japan to lower the intraocular pressure in simple glaucoma, and to improve glaucomatous scotomas, but the original work was not available to me for study and evaluation.[75,134]

Miotic parasympathomimetic drugs continue to be the principal means for medical management of most types of glaucoma, and there is a continuing effort to discover new drugs in this category which may have advantages in duration of action, in reduced tendency to sensitize, and in improved stability, while maintaining maximum effectiveness in lowering intraocular pressure. Additional observations have been made on a new miotic drug mentioned in last year's review,[66] decamethylene-bis-(N-methylcarbaminoyl-m-trimethylammonium phenol), which is a long-acting inhibitor of cholinesterase providing miosis for 5 to 10 days after local application of a 1% aqueous solution. Recent observations on glaucomatous patients indicate that the duration of action and intensity are similar to that of isoflurophate (DFP), and that the most useful concentrations clinically are 0.2% to 0.3%, which may be employed once a day.[63] Another cholinesterase inhibitor having similar miotic properties and effectiveness in control of glaucoma is the compound 2-diethoxyphosphinylthioethyltrimethylammonium iodide (Echothiophate, 217-MI, Phospholine iodide). This drug is suitably employed in 0.1% to 0.25% aqueous solution applied at

a rate varying from twice daily to twice weekly, according to the individual requirements.[86] In general this drug resembles isoflurophate in mode, potency, and duration of action. Both of the new long-acting cholinesterase inhibitors have the practical advantage over isoflurophate that they are soluble and reasonably stable in aqueous solution and thereby obviate the necessity for using an oily vehicle. The usual oily solution of isoflurophate has a minor disadvantage of causing unpleasant oiliness of the lids and a major disadvantage that contamination of the oil solution by water, such as by tears transferred by an eye-dropper to the patient's bottle of drops, may cause hydrolysis and loss of miotic activity without the patient or ophthalmologist being aware of it. Another cholinesterase-inhibiting miotic about which considerable has been written in the past, diethyl-*p*-nitrophenylphosphate (Mintacol, Ortho), is useful in aqueous solution but has intensity and duration of action shorter than that of isoflurophate, more like that of physostigmine. Clinical observations have been reported on antagonism between this drug and atropine.[104]

As a general rule, the initial screening and testing of potential miotic drugs is carried out in animal eyes before the most promising are given clinical trial; the methods for assay of cholinesterase-inhibiting activity in animal eyes have been subjected to close examination, and results for numerous compounds have been compiled.[126] The compound monoethylamide of bis-diethylphosphoric acid has been reported to cause miosis in rabbits, but comparative data are not available, and apparently clinical tests have not been made.[136] Investigators in Russia seem to be considerably interested in the miotic properties of compounds of this type; reports of tests of series of related compounds on rabbit eyes have been published, and several compounds have been found to be potent miotics, but none appear to have properties outstandingly different from previously described cholinesterase-inhibiting phosphate esters.[115,135]

The direct-acting parasympathomimetic miotics, as distinguished from the cholinesterase inhibitors, have also received some attention in the period under review. The actions of nonaromatic quaternary ammonium compounds on the eye have been comprehensively reviewed, and data have been supplied on a number of compounds previously untested for pupillary effects.[64] In comparisons of homologous series of these compounds, maximum miotic activity was found to be associated with molecular structures having dimensions similar to acetylcholine, as exemplified by amyl, ethoxyethyl, propoxymethyl, carbamyl, 5-methylfurfuryl trimethylammonium compounds, and the compound known as 2268F. Clinical evaluation of 2268F, trimethyl(2-methyl-1,3-dioxolan-4-ylmethyl) ammonium iodide or chloride, was undertaken because of the extraordinary muscarinic miotic activity of this substance. It was found to be very effective in reducing the intraocular pressure in primary glaucoma when applied as eye drops.[64] However, its clinical applicability was found to be limited because of systemic side-effects, and it appeared for this reason to have no fundamental advantage over miotic drugs which are in current use.[64] Tests of alkylated derivatives of the natural muscarinic alkaloid arecoline, failed to bring forth any derivative having greater miotic effectivness than areocoline itself.[145] Pharmacologic studies on preparations of animal iris and ciliary muscle have been reported, adding to basic information on the subject of miosis and accomodation.[84,95] A new physiologic component of rabbit iris has been discovered and named Irin; this substance is of considerable interest because it causes smooth muscle to contract but is not identifiable with known physiologic substances having this property, such as choline esters, 5-hydroxytryptamine, Bradykinin, or Substance P.[6] Whether this substance may find some clinical application as a miotic remains to be seen.

The mechanism by which miotic drugs lower the intraocular pressure has intrigued investigators since the first observations on

physostigmine in the 19th century, and this continues to be a subject of study. It has long been postulated that in angle-closure glaucoma the miotic drugs may succeed in opening the angle through pupillary constriction and that in open-angle glaucoma the ciliary muscle, through its attachment to the scleral spur and corneoscleral trabecular meshwork, may cause the channels through this tissue to enlarge and to permit an easier outflow of aqueous humor. Measurements of facility of outflow in recent years have provided supporting evidence for an increase in ease of outflow under the influence of miotics. It has generally been recognized that miotic drugs lower the pressure more in glaucomatous eyes than in normal eyes, and this has been substantiated recently [67]; the basis for the difference in responsiveness is still under investigation. An especially pretty morphologic demonstration of the mechanical effects of contraction of the ciliary muscle under the influence of pilocarpine has been made by sectioning the angles of monkey eyes both meridionally and tangentially and comparing these with contralateral eyes of the same animals under the influence of cycloplegia.[51] These studies strongly support similar earlier observations that the ciliary muscle contracted under the influence of physostigmine and that the corneoscleral trabecular meshwork appeared to be spread out, with enlargement of the openings in this tissue. These changes have been shown to be associated with increased facility of outflow.[51]

The influence of drugs related to epinephrine on intraocular pressure appears to have received relatively little attention in the year under review. Confirmation has been provided that a significant decrease in intraocular pressure may be obtained in glaucoma simplex and secondary glaucoma by application of phenylephrine (Neo-Synephrine, Isonephrine), but that in eyes with narrow angles mydriasis induced by this or other mydriatic drugs can cause a rise of pressure.[26,56] Ephedrine was found to have little or no effect on the intraocular pressure in normal eyes of young persons when 1 drop of 4% solution was applied.[96]

Among drugs purported to cause an increase in intraocular pressure,[41,133] calcium phosphorylcholine was mentioned with some scepticism in last year's review [66]; more recent clinical trials have indicated that subconjunctival injections of this drug are ineffectual in treatment of post-traumatic hypotony.[41] Occasional increases in intraocular pressure have been attributed to corticotropin (ACTH) and to the corticosteroids, but the evidence has not been at all convincing that these drugs constitute any general hazard with respect to the intraocular pressure. A recent report on three patients receiving steroid therapy for arthritis, and coincidentally having glaucoma, carries little additional weight in this respect. No evidence has been provided in this most recent report actually to inculpate the steroids.[37]

Mydriatic-Cycloplegic Drugs.—In this category, drugs having varied properties are in clinical demand for different purposes. Short-acting mydriatics are in demand as an aid to examining the fundus; short-acting cycloplegics are advantageous in certatin cases for refraction, and long-acting mydriatic and cycloplegic preparations are usually desirable in treatment of inflammatory conditions in the eye. A comparative study of the mydriatic and cycloplegic preparations commonly employed clinically has recently been carried out with particular attention to the differences in response between eyes of white and Negro patients. Among the drugs tested for mydriasis in Negroes, ephedrine and cyclopentolate (Cyclogyl) were relatively ineffectual in comparison with phenylephrine, and the widest mydriasis was obtained in both light and dark eyes by means of scopolamine, atropine, or homatropine. Cycloplegia was both uniformly and completely induced in all types of eyes by means of scopolamine. Cyclopentolate was less effective in Negro eyes than has been previously reported, and homatropine did not have significant cycloplegic effect in Negroes.[17] Substitutes for

atropine have been sought from time to time with the object of discovering substances which might have similarly intense mydriatic cycloplegic effect of long duration appropriate in the treatment of uveitis but which might have advantages in less systemic toxicity and less tendency to cause local sensitization. One potential substitute, Lachesine, is no longer manufactured, and oxyphenonium (Antrenyl) has been recommended as a good substitute on the basis of clinical experience showing that this drug has intensity and duration of action similar to those of atropine but exhibits no cross sensitization and has little tendency to induce sensitivity.[117] A comparison in rabbit eyes of several other potential substitutes for atropine, evaluating particularly their local and systemic toxicity, indicated that penthienate bromide was particularly promising, and clinical trials have indicated that this drug is equal to atropine and is not irritating, even in eyes which have developed a sensitization reaction to atropine.[78]

In a systematic study of the action of nonaromatic quaternary ammonium compounds on the eye, a new instance of inversion of miotic to mydriatic activity has been observed.[64] In a series of alkylether-substituted trimethyl and triethyl ammonium compounds, it was found that when the alkylether portion of the molecule was of relatively low molecular weight the compounds induced miosis but when the size of this portion of the molecule was increased to 2-butoxyethyl and 2-butoxypropyl the compounds caused mydriasis instead of miosis. The effect was observed both in guinea pig and human eyes but was not of sufficient intensity or duration to be worth while for clinical application.

Pharmacologic studies not having direct therapeutic applicability have been made on pupillary responses to drugs which are best known for their action on the central nervous system. Administered systemically to normal human beings, lysergic acid diethylamide (LSD) causes mydriasis and chlorpromazine hydrochloride causes miosis, but there is considerable variation from person to person.[20,76,121] Meperidine (Demerol) and secobarbital have little influence on the pupil under similar circumstances. The mydriatic influence of LSD is believed to be a sympathicotonic effect, whereas chlorpromazine may have a predominately peripheral adrenolytic action.

Corticosteroids and Other Anti-Inflammatory Agents.—Two particularly comprehensive surveys have been provided, one by Woods discussing not only principles but also practical applications of steroid therapy[159] and the other by Nielsen and Kirby covering all aspects of the modern treatment of uveitis.[99] Among the conclusions arrived at are that application of corticosteroids to the anterior segment of the eye is without benefit in inflammatory conditions of the posterior segment. When systemic administration is necessary, the corticosteriods are more convenient than corticotropin because of the ease of oral administration, but in some instances of particularly severe inflammation of the posterior segment corticotropin may be more effective. An advantage of corticotropin is that it has a prolonged action and does not suppress the adrenal cortex. Systemic therapy with either type of substance is contraindicated in the presence of tuberculosis, peptic ulcer, severe hypertension, cardiac disease, diabetes, or an acute infection for which there is no specific treatment. Following are quotations of some of Wood's most cogent observations, some verbatim and some paraphrased. Topical (and systemic) therapy with corticosteroids and the parenteral use of corticotropin give favorable results in such external ocular inflammations as contact dermatitis, rosacea keratoconjunctivitis, allergic conjunctivitis, marginal corneal ulcers, phylectenulosis, and allergic keratoconjunctivitis. Such treatment is without effect in such conditions as nodular episcleritis and pemphigus. It apparently accelerates dendritic keratitis and fungus infections of the conjunctiva or cornea. In various other external conditions, episcleritis, rheumatic nodules, and collagen

diseases of the eye, the therapeutic effect is irregular. Temporary regression in thyrotropic exophthalmos and in pseudotumor of the orbit may occur irregularly. In nongranulomatous iridocyclitis and posterior nongranulomatous uveitis these agents reach their highest usefulness. The therapeutic response of iritis to topical therapy and of posterior nongranulomatous uveitis to systemic therapy is prompt, and, if treatment is continued over the natural life of the inflammation, the results simulate a cure. Hormonal therapy, especially corticotropin administered by intravenous drip, is the very best treatment as yet available for sympathetic ophthalmia. Once it is controlled by intravenous administration of corticotropin, intermittent courses of corticosteroids are indicated for a year or longer to prevent recurrences. Intensive hormonal therapy is indicated in ocular sarcoidosis, but it does not prevent recurrences when treatment is terminated. The long-continued topical use of corticosteroids, may, however, prevent recurrences once the local disease has been controlled by systemic hormonal therapy.

The common and current practice among manufacturers of combining various corticosteroids with antibiotics has been condemned by one writer as being a dangerous practice for the physician to accept, particularly in the treatment of viral, bacterial, or fungus infections, where corticosteroids may be contraindicated.[150] On the other hand, claims have been presented that a combination of a corticosteroid with an antihistaminic is useful for relief of allergic ocular conditions, relieving the symptoms of lacrimation, burning, and itching.[1] That not all cases of herpes simplex of the cornea are made worse by corticosteroid therapy has been noted in the treatment of a considerable variety of inflammations of the anterior segment with hydrocortisone, with generally beneficial results but with no effect in three cases of herpes simplex.[120] In the case of epidemic keratoconjunctivitis it has been claimed that if a hydrocortisone-neomycin ointment is employed before the fourth day of the disease a corneal lesion is rarely observed, whereas without this treatment 70% were observed to develop lesions in the cornea.[144]

The discomfort which may be caused by crystals in suspensions of corticosteroid drugs has been avoided by the use of prednisolone alcohol in solution, and this is said to give good results clinically, although no clinical comparisons with other preparations have been presented.[85]

Besides the corticosteroids, a variety of other substances have been investigated experimentally or employed clinically for reducing inflammatory reactions. Experimentally, the infiltration of the cornea and of the skin by leukocytes which ordinarily occurs in response to local injury is found to be delayed for about 24 hours when rabbits are poisoned systemically with iodoacetate. This is apparently not an effect of the poison on the cornea or skin itself, for local application of iodoacetate does not retard leukocytic infiltration.[74] The infiltration of leukocytes into the cornea after injury can be retarded experimentally by local application of sodium salicylate or soybean trypsin inhibitor.[154] What the clinical import of these observations may be remains to be seen. Clinically, it is claimed that phlyctenular disease of the eye can be cured by local and systemic administration of aminosalicylic acid.[111] Rather enthusiastic claims have been made for treatment of a wide variety of inflammatory conditions of the front and back of the eye by means of cyanocobalamin (vitamin B_{12}) and related substances, but these claims are difficult to evaluate at present. In particular, herpes keratitis and retrobulbar neuritis improved under this treatment in certain cases, but these conditions are also known to improve without treatment in some cases.[80,114] Subjective relief has been reported in Sjögren's syndrome by intravenous injections of cocarboxylase and administration of B vitamins, but there was no change in the results of the Schirmer test nor in staining of the

cornea, and the symptomatic relief was transitory.[38]

Other clinical observations which are difficult for me to evaluate concern the use of trypsin. As noted in last year's review,[66] intramuscular injection of trypsin has been recommended for treatment of hemorrhages in and about the eye. Earlier clinical reports have indicated that edema is absorbed promptly in some cases of ocular trauma, but in a recent clinical study poor results have been reported in patients with posttraumatic hyphema.[87] Experimentally, confirming in rabbits the previous negative results obtained in treatment of hyphema in guinea pigs, tests of the influence of trypsin on disappearance of blood from the anterior chamber have shown no increase in rate of disappearance under treatment with this enzyme.[128] Clinically, good results have been claimed for trypsin in treatment of patients threatened with retinal venous occlusion,[57] but no benefit has been obtained in retinopathy due to diabetes or kidney disease.[57,82]

Influence of Drugs on Retinal and Uveal Vessels.—In last year's review[66] mention was made of treatment of senile macula degeneration and of retinal arterial occlusions by administration of heparin. It was noted that adequate controls were lacking in the first application and that the second application involved much speculation. Now, other studies have appeared on the effects of anticoagulants on vascular abnormalities in the eye. In particular, one clinical study has been presented on the treatment of 75 patients having retinal venous occlusions, usually in accompaniment with arterial sclerosis and hypertension. Primary glaucoma was present in only 10% of the cases. Approximately half of the cases were treated with heparin for two to three weeks, or sometimes with bishydroxycoumarin (Dicumarol), and by continuing twice-weekly administrations of heparin and vitamin E for months or years. The results in the cases treated in this way are reported to have been much better than in untreated controls.[149] The results in this study are considerably more favorable than have been reported by others with anticoagulant therapy for retinal venous occlusion, and the authors attribute this to the fact that they have used principally heparin in the early treatment, whereas others have used principally bishydroxycoumarin. Other investigators, employing a synthetic mixture of polysaccharide sulfuric esters resembling heparin in treatment of retinal venous occlusion, report that favorable results were obtained when treatment was started early but also that worth-while effects were thought to be obtained even several months after the original occlusion.[98] On the other hand, the fovea was disturbed by new hemorrhage in 5 of 79 eyes during treatment.[98] In this study no untreated group was included for comparison. Primary glaucoma was noted in less than 10% of the cases, and in these cases conditions became worse in spite of treatment. Only one case of secondary glaucoma was observed, occurring five months after the start of treatment. It seems remarkable to me that the incidence of secondary or hemorrhagic glaucoma in this series of cases was so very low in comparison with the incidence generally reported in cases of occlusion of the central retinal vein; this would be not so surprising if most of the occlusions were branch rather than central vein occlusions. In treatment of diabetic retinopathy, trials of bishydroxycoumarin, α-tocopherol, lipotropic and flavonoid substances, and trypsin have provided no definite benefit.[82] Careful control of the underlying diabetes appears to be the best that can be offered so far in preventing this kind of retinopathy.

In treatment of central serous retinopathy the injection of tolazoline (Priscoline) intramuscularly has been reported to have given promising results in nine patients,[24] but in a condition which often improves without treatment it is difficult to evaluate any form of therapy without a large series

of cases. The influence of numerous drugs on the angioscotomas of patients having various disturbances of the retinal circulation has been described, and interpretations are offered on the supposed site and mode of action of these drugs, based on a series of assumptions regarding the significance of changes in the angioscotoma and on the role of various portions of the retinal vascular tree.[160] In another pharmacologic study of angioscotomas it has been determined that tobacco smoking widens the angioscotoma and that this effect is independent of whether or not the tobacco contains nicotine. In fact, mechanical irritation of the throat was found to have the same effect on the angioscotoma as did smoking.[93]

Chemotherapeutic and Antibiotic Substances.—A comprehensive survey has been provided of current opinions and practices in the chemotherapeutic and antibiotic treatment of various forms of uveitis.[90] In this survey are discussed treatments for uveitis caused by syphilis, tuberculosis, brucellosis, toxoplasmosis, trypanosomiasis, actinomycosis, blastomycosis, cryptococcosis, histoplasmosis, and onchocerciasis.[90] Case reports of results of treatment of ocular toxoplasmosis in 14 patients support previous reports of beneficial influence from pyrimethamine (Daraprim).[52]

In patients with tuberculous meningitis a considerable increase in the incidence of choroiditis has been reported as a consequence of improved treatment and survival from the meningeal infection. With treatment with streptomycin and isoniazid an incidence of 40% to 50% is reported. The same antibiotic and chemical treatment is said to have a favorable effect on the choroidal lesions.[43]

The influence of various ointment bases on chloramphenicol in ophthalmic application has been exhaustively studied, both in human and in rabbit eyes. From a comparison of 25 different ointment bases it was concluded that the most effective and most suitable vehicles for application of chloramphenicol for external bacterial infections of the eye were vegetable oils or water-in-oil emulsions, which were much more efficient than paraffin ointment bases. On the other hand, for deeper penetration into the eye, ointment bases such as oil-in-water emulsions or water-soluble polywaxes were more effective than the fatty ointments. The investigators recommend that the appropriate base be chosen for either superficial or for deep infection.[116]

Various recommendations for treatment of extraocular infections have been made on the basis of clinical experience for erythromycin ointment,[70] for Primycin and penicillic acid,[4] and for a cationic surface agent, Desogen (Geigy).[125] Erythromycin is said to be of value particularly against Gram-positive bacteria, although it does occasionally cause allergic reactions.[70] Primycin is said to be effective against Gram-positive bacteria, and penicillic acid, to be active against Gram-negative bacteria.[4] These substances are considered to be too toxic for systemic use, and it is urged that they be given preference for local use, so as to avoid sensitizing the patients to antibiotics which might sometime be needed for systemic administration. Desogen has been recommended to replace silver nitrate for prophylactic treatment of the eyes of newborn infants as a result of a clinical survey and bacteriological investigation.[125]

A pioneer study in the chemotherapy of tumors of the eye has been reported by Reese in treatment of retinoblastoma by means of triethylenemelamine in combination with radiation.[113] Treatment by combining radiation and systemic administration of triethylenemelamine was found to be more effective in retarding growth of tumor and prolonging life than was radiation alone. Furthermore, use of the cytotoxic chemical permitted the dosage of radiation to be decreased, with the advantage that hemorrhages into the vitreous were thereby avoided and visual results were better. Also, with reduced radiation the resultant cosmetic deformities were less.

Intramuscular administration of triethylenemelamine was found to be more effective than oral administration, and preliminary observations suggested that intracarotid administration might permit more selective action in the eye.

Pre- and Postoperative Medications.—Several drugs have been studied primarily for the purpose of preparing the patient for operation on the eyes or for reducing or correcting complications associated with operations on the eyes. In particular, chlorpromazine has received considerable attention and approval as a preoperative medication.[2,71,77] Judging from the results in several series of intraocular operations it appears that chlorpromazine provides improved sedation and relaxation and reduces nausea and vomiting significantly. It has been recommended that 50 mg. of the drug in either a single or divided dosage be administered within a half hour preoperatively, in addition to the usual barbiturate or other sedative. No serious complications are noted.

Several observations on the effect of succinylcholine (Anectine) on the extraocular muscles have been published in recent years, unanimously indicating that, although this drug relaxes skeletal muscle, it causes a contraction of human extraocular muscles and induces transitory rise in intraocular pressure. Further reports have appeared substantiating these findings, and concurring in the view that this drug is not suitable for use during intraocular surgery because of the potential hazard from contraction of extraocular muscles.[42]

In an effort to relieve the patient of pain at the time of ocular surgery and during the first 8 to 10 hours following operation, a search has been made for a long-acting local anesthetic, and this need has been met in part by suitable choice of anesthetic agent and by injecting additional amounts of the agent as required postoperatively by way of an in-lying polyethylene tube in the orbit.[127] Primacaine (2′-diethylaminoethyl-2-butoxy-3-aminobenzoate) hydrochloride in 1.5% solution was found to provide anesthesia for approximately one hour longer than did 2% lidocaine or 2% procaine injected retrobulbarly in patients. Primacaine at this concentration has produced no toxic effects and has proven very satisfactory. No notable difference in duration of anesthesia was noted when hyaluronidase was added. An interesting observation is reported that when pilocarpine was applied to the eye at the time of operation it caused a significant increase in the amount of postoperative pain.[127]

The use of acetazolamide pre- and postoperatively has been evaluated in patients by several observers in recent years, with varied conclusions. In the year under review, administration of this drug was not found to alter the incidence of hyphema following cataract extraction, nor did it alter the incidence of flat anterior chamber following this operation.[148] On the other hand, it is reported that in 50 cases of iridencleisis in which acetazolamide was administered, compared with another 50 cases in which the drug was not employed, the incidence of flat anterior chamber up to the fifth postoperative day was 42% in the control series and only 6% in those treated with acetazolamide. Despite this, the ultimate result of establishing adequate drainage for the control of glaucoma was satisfactory in 80% of the controls, compared with 76% treated with the drug.[3] It seems to me that convincing evidence or a clear rationale for the postoperative use of acetazolamide in the absence of elevated intraocular pressure has not yet been provided.

A postoperative treatment which has been logically developed and convincingly recommended is the mydriatic treatment of secondary shallowing of the anterior chamber following cataract extraction.[156] The condition under consideration is not the flat or shallow anterior chamber which may be present immediately postoperatively and in most instances is due to a leak in the wound; the condition for which mydriatic

treatment is efficacious is the shallowing of the anterior chamber that develops several days or even weeks after cataract surgery and appears to be associated with hypotony and choroidal detachment and is not influenced by acetazolamide. The treatment which has been found more rapidly effective than any other is induction of extreme mydriasis by means of cycloplegics such as scopolamine or atropine in conjunction with sympathomimetic drugs such as cocaine plus 1% epinephrine or 10% phenylephrine. The chamber has been observed to deepen within 30 to 90 minutes after induction of extreme mydriasis, and in most instances the chamber has not again become shallow. However, in some instances, when the pupil was allowed to constrict, the chamber again shallowed and wide dilatation was required to deepen it again. In none of the eyes treated in this manner has it been necessary to do posterior sclerotomy or to inject air into the anterior chamber. Some observers have also reported beneficial effects from miotics in this same condition, and it is suggested that miosis may also have succeeded in breaking adhesions between the vitreous and iris. It is recommended that to prevent pupillary block and shallowing of the anterior chamber following cataract extraction an adequate iridectomy and good mydriasis should be provided for some weeks postoperatively.[156]

In the interests of minimizing bleeding associated with intraocular surgery, some attention has been given to an oxidation product of epinephrine, carbazochrome (adrenochrome), which is said to reduce leakage from capillaries. Results in a controlled clinical study were not really conclusive; bleeding into the anterior chamber following cataract extraction occurred in 16% of 63 patients treated with the drug and in 22% of the same number of untreated patients.[45] Experimentally in albino rabbits the drug does appear to have some protective effect on the blood-aqueous barrier when paracentesis is performed; it is reported to delay the appearance of a test dose of flurescein in the aqueous in comparison with untreated controls.[100] However, this latter observation relates to changes in permeability rather than to actual bleeding.

Pharmacologic Influences on the Cornea. Apart from the treatments of corneal disease mentioned under the headings of corticosteroids, chemotherapeutics, and antibiotics, the principal pharmacologic attention to the cornea in the period under review seems to have been in connection with topical anesthesia. As is well known, certain local anesthetic agents such as procaine are highly effective on injection into tissues but when applied to the surface of the cornea are poorly absorbed and cause only slight anesthesia. Primacaine seems to be in this same category.[127] Many substances which increase the permeability of the epithelium improve the anesthetic effectiveness of poorly penetrating anesthetic compounds; among those which are reported to have this effect are preservative substances[81] employed in collyria and hexamethylenetetramine.[112] Irrigation of the cornea with various solutions and with water has been observed to interfere with anesthesia, whereas drying appears to favor it.[31] It has become well known that surface anesthetic agents commonly interfere with regeneration of corneal epithelium, and for this reason it is generally felt that the repeated or continuing application of local anesthetic agents is contraindicated in the treatment of corneal injuries. A number of experimental studies in the past have provided the basis for this view, and clinical observations of seriously delayed healing have substantiated and reinforced it. There has, however, been moderate variation in the results of experimental studies by different observers employing different types of injury, different animal species, and different methods of evaluation. New data have been obtained in a recent comparison of the influence of a series of local anesthetics on regeneration of epithelium of the rat cornea. In this

investigation multiple fine needle-point injuries were made in the epithelium and local anesthetics in the concentrations ordinarily employed clinically were applied every 15 minutes for 3 hours. The corneas were then examined microscopically in flat preparation, and by this technique it appeared that healing was prevented by anepaine (Amylsine), butacaine (Butin), cocaine, benoxinate (Dorsacaine), phenacaine (Holocaine), dibucaine (Nupercaine), and Ophthaine. Healing was delayed slightly by tetracaine, but the epithelium appeared to be regenerating normally in the presence of piperocaine (Methycaine) and lidocaine (Xylocaine).[91]

In band keratopathy associated with Still's disease good clearing of the corneas has been observed in four eyes of two patients following removal of the epithelium and local application of edathamil sodium (EDTA, Versene).[139] In another case in which band keratopathy was associated with hypercalcemia rather than iridocyclitis, the cornea was observed to clear spontaneously after the cause of the hypercalcemia had been corrected.[35] Treatment with edathamil sodium may, therefore, best be reserved for those cases in which the underlying cause of band keratopathy cannot be completely removed or corrected and for use in lime burns of the eye, as indicated under the heading of toxicology.

Miscellaneous.—Mentioned in last year's review[66] was an observation on the fact that patients were relieved of symptoms of ocular asthenopia by placebo collyria as effectively as by a proprietary mixture containing small amounts of digitalis, suggesting that psychotherapeusis was the basis for the effect of both preparations. Now a polemic rejoinder has appeared defending the digitalis preparation but in no way reducing the significance of the earlier observation that a placebo collyrium was just as effective.[130]

Ophthalmic Toxicology

Cornea and Conjunctiva.—Information on toxic disturbances of the cornea and conjunctiva during the year under review has been derived largely as a by-product of more general toxicologic studies and from occasional case reports. One experimental investigation has been directed specifically toward elucidating some of the biochemical characteristics of acid injury of the cornea.[69] In this study it was determined that hydrochloric acid caused an immediate opacification of the cornea in rabbits before any change in water content was detectable but that later increase in opacification was associated with swelling of the cornea. Following an injury from acid of moderate severity from which recovery was possible, it was found that both glycolysis and oxygen uptake were markedly inhibited immediately after injury, probably as a result of damage to the corneal epithelium. Oxygen uptake and glycolysis returned to normal when the epithelium regenerated, and until the epithelium had regenerated it was not found possible to restore normal metabolic activity by artificially supplying substrates and intermediates of carbohydrate metabolism to the cornea.[69] A very detailed study of the caustic effect of solid silver nitrate on the cornea has been made in rabbit eyes, and the influence of many variables on the tissue reactions occurring during the first 6 to 24 hours has been examined.[67] Possibly the most unusual observation has been that when a rabbit eye has been enucleated and the cornea cauterized with silver nitrate and then the eye has been placed back in the orbit of the animal, a series of changes occur in the cornea which are histologically identical with those which result from cauterization of the eye in situ. In dead animals a similar procedure produces no histologically demonstrable inflammatory reaction.[67]

The problem of irritation of the eyes by smog of the type encountered in the vicinity of Los Angeles continues unsolved and unmitigated, but more is being found out about the materials responsible for this irritation. An experimental study in which

dogs were exposed to ozone for six hours daily for a year at concentrations slightly higher than are attained in urban atmospheres revealed no disturbance of the eyes, although these same conditions did cause injury to the lungs.[142] A more definite lead concerning the eyes was found in a study of automobile exhaust, in which it was found that under experimental conditions the exhaust of automobiles in concentrations similar to those in the atmosphere of Los Angeles caused eye irritation of the type familiar there, and as the hydrocarbon content of the exhaust was increased the eye irritation became still worse.[48] Aldehydes have been among the various substances suspected of irritating the eyes in smog, but a recent experimental study on human subjects has shown that the irritant and lacrimatory properties of different aldehydes vary widely and that there would be no value in attempting to relate indiscriminate "aldehyde content" of smog samples to irritancy without identifying the aldehydes present. Of the aldehydes tested in this particular investigation, acrolein, crotonaldehyde, and formaldehyde were found to be the most irritant and lacrimatory; acetaldehyde was only slightly irritating, and propionaldehyde, butyraldehyde, and isobutyraldehyde were nonirritant at similar concentrations in air.[137]

During the past 25 years occasional reports have appeared of a peculiar type of keratitis epithelialis resulting from exposure to vapors of organic solvents. This keratitis is characterized by the appearance in the human corneal epithelium of fine vacuoles visible by slit-lamp biomicroscope. These characteristic vacuoles may be present with slight symptoms, or there may be considerable irritation in the severest cases. The circumstances of the appearance of this special kind of keratitis among industrial workers has cast the principal suspicion on *n*-butyl alcohol (butanol) as the principal cause. Two good résumés of the subject have recently appeared, and the authors of both have contributed their own studies of the condition in animal eyes.[129,140] By exposure of cats to high but sublethal concentrations of various solvents it has been possible to produce typical fine vacuoles in the corneal epithelium in less than six hours, and these vacuoles spontaneously disappear by the next day when exposure is discontinued. In these experiments it was not found possible to produce vacuolar keratitis by means of butanol, but this condition could be induced by means of toluol, xylol, methyl acetate, ethyl acetate, and butyl acetate.[12] Exposure of rabbit eyes to air saturated with butanol vapor caused injury of the corneal epithelium within hours, characterized by numerous small defects in the epithelium in the palpebral fissure without damage to the corneal stroma, but in no instance were described in human eyes. Recovery was rapid following removal of the animals vacuoles seen such as have been repeatedly from the vapor.[140] In contrast to the injurious effect obtained with butanol vapor, no corneal damage was caused in rabbits by exposure to high vapor concentrations of ethyl acetate, ethyleneglycolmonoethyl ether (Cellosolve), or ethyleneglycolmonoethylether acetate (Cellosolve acetate).[140] It is possible that there are species differences in corneal response to various solvents, and the cause of the typical vacuolar keratitis seen in human eyes may be established only by observing the effects of controlled exposures of human volunteers to the vapors of pure solvents which are suspect. The evidence obtainable from results of industrial exposure is usually inconclusive, because of the presence of a mixture of several substances in the air.

A modern industrial irritant to the eye is encountered in the preparation of polyurethane plastic foam, which is becoming more and more widely used as an insulator and packing material. The polymerized plastic is physiologically inert, but the isocyanates from which the plastic is made are strongly irritant to all the mucous membranes, especially to the eyes and

respiratory tract. In particular toluene-2, 4-diisocyanate (TDI) vapor is irritating, and experimentally it is found to be damaging to the corneal epithelium in rabbits.[161] Other types of plastics sometimes give rise to irritating and lacrimogenic breakdown products. Formaldehyde is said on occasion to be liberated from urea or melamine-formaldehyde resins which are applied to cotton and synthetic fabrics to make the cloth crease-resistant; sufficient concentration of formaldehyde is reported to have been released in the vicinity of racks of dresses in clothing stores to cause annoying irritation.[92] Exposure to heat causes polyvinylchloride plastics to give off fumes which contain hydrochloric acid and irritate the eyes.[49]

Some uncertainty has existed concerning the effects of chlorine dioxide on the eyes since the first toxicologic report on this substance, in 1902. In the earliest cases reported chlorine dioxide gas was mixed with other gases, and there has been uncertainty as to what portion of the effects described to attribute to the chlorine dioxide. A recent report presents three cases of respiratory involvement from exposure to chlorine dioxide alone and mentions "halo" phenomena as occurring in the eyes in some cases, but this does not go far in clarifying the ophthalmic aspects of the reaction.[61]

An unusually severe injury of the eye by zinc chloride has been described in which the accidental application to the eye of only a single drop of a 50% solution of this chemical in water caused severe pain and led to much edema of the cornea, resulting ultimately in considerable turbidity and vascularization, despite treatment with mydriatics and cortisone. Large peripheral spoke opacities are described in the lens in this case, but it was not made evident whether these were attributable to the chemical burn.[128]

Sensitivity to iodides is known to cause a number of ocular reactions; these have been recently reviewed, and three additional cases have been reported in illustration.[58] In two of these cases systemic administration of iodides led to acute onset of severe keratoconjunctivitis, in one case accompanied by hemorrhagic iritis and vitreous opacities; in the third case, local application of iodine in the treatment of herpes in a sensitized person caused generalized urticaria, edema of the lids, follicles of the conjunctiva, and bullae of the cornea. Discontinuance of the exposure to iodides appears to have been the most important factor in the treatment.

Recent observations on injuries to the eyes by tear gas, in particular by ethyl bromoacetate, substantiate earlier observations that tear gas vapor may cause corneal edema accompanied by wrinkling of Descemet's membrane but that in mild cases usually recovery is spontaneous. However, as has been reported in numerous instances before, exposure to high concentrations of tear gas may cause permanent corneal scarring and opacity.[44]

From Russia, in a systematic investigation of ocular effects of exposure to a wide variety of chemicals in industry, specific attention is called to the fact that dry diphenyl guanidine powder causes punctate corneal epithelial defects and edema of the lids and conjunctiva.[143]

Several articles have become available on treatment of chemical burns of the eye.[46,49,110,122] These generally reiterate the usual teaching in regard to prompt irrigation in first-aid treatment. In regard to later treatment the recommendations which are made generally stem from uncontrolled clinical observations. Such is the case in two discussions of the treatment of lime burns of the eye.[39,110] One author in the course of treating 88 cases of lime burns in several years has tended progressively toward conservative medical treatment, abandoning transplantation of mucosa from the lip and resorting to corneal transplantation at only a late stage.[110] The same author favors the use of vasodilator substances and recommends repeated subconjunctival

injections of tolazoline directly under the burned conjunctiva; no experimental support is provided to establish the value of the treatment recommended, but good clinical results are reported.[110] Another author recommends subconjunctival injections of procaine, but his theory seems weak and his clinical data are unconvincing.[30] Neither author mentions experience with edathamil sodium (EDTA) as an aid in quick cleansing of lime from the cornea and conjunctiva; it is employed in many clinics both for this purpose and for clearing superficial calcification of the cornea in band keratopathy.[65]

The toxic effect on the cornea when copper is inserted into the anterior chamber of rabbits has been studied experimentally, and it has been made evident that changes produced in the cornea are the result of the chemical action rather than a result of mechanical trauma; it has been shown that iron particles inserted in the same manner cause much less reaction. When particles of pure copper are inserted into the anterior chamber, the cornea becomes turbid within 24 hours in the vicinity of the metal; in the course of 7 to 10 days there is exudation into the anterior chamber, and the whole cornea becomes cloudy and vascularized.[106]

Lens.—The question is again brought up as to whether occupational exposure to vapors and dusts of naphthalene can cause cataract in human beings. It is well known that experimentally in animals large doses of naphthalene do cause cataract, and there are rare cases in which ingestion of several grams of naphthalene has been reported to cause uveitis and cloudiness of the lenses in patients. However, whether a significant hazard is connected with exposure to naphthalene vapor industrially remains open to question. In a survey in Italy of workers employed in manufacture of a dye intermediate from naphthalene, pinpoint and diffuse opacities of the crystalline lens were noted in 8 of 21 workers, with a preponderance in the younger age group.[59]

Alloxan is a substance which induces diabetes and cataract in animals and has been employed in many studies concerned with cataract formation. A very thorough study has recently been published on the morphology of incipient alloxan-induced cataract in animals, both by biomicroscopy and by microscopy of lens sections.[124]

In recent years a series of articles on experimental production of cataracts by various chemicals has issued from a single laboratory. Some of these articles have borrowed rather heavily from the earlier writings of others, but most of the experimental work appears to have been original.[101,102,147] In one of these studies the experimental production of cataract by dinitrophenol has been investigated, and it is reported that several of the compounds that were earlier found to be cataractogenic in chickens can also induce cataract in scorbutic guinea pigs.[101] In other articles of the series a thesis has been developed that certain quinoid substances may have an intermediary role in the induction of cataracts by a variety of agents and natural causes. Thus, claims are made, on the basis of tests in vitamin C-deficient guinea pigs, that quinones which are metabolites of naphthalene and of tyrosine are cataractogenic and, furthermore, that administration of tyrosine plus various ketogenic substances causes cataracts. In accord with the same thesis, a claim is made that cataractogenesis by alloxan, by dinitrophenol, and by galactose is associated with an abnormal metabolism of tyrosine, and that in human beings "the onset of senile cataracts is closely related to the abnormal metabolism of tryptophane."[102] These claims must, of course, be adequately evaluated by other investigators. If the concepts presented should prove valid, they would constitute a considerable advance in the study of cataract production. In recent years it has become well established that administration of iodoacetate to experimental animals is peculiarly toxic to the eye, causing changes in several of the ocular tissues.

Most attention has formerly been given to the effects upon the retina, but it is also recognized that iodoacetate causes cellular exudation in the aqueous humor and vitreous and causes cataract. These latter effects have attracted attention recently particularly because of a close resemblance to the effects induced by high-intensity ionizing radiation. To compare these chemical- and radiation-induced injuries a thorough morphologic study has been carried out, substantiating their similarity but revealing that the response to iodoacetate in the anterior segment is somewhat complicated by a tendency of this chemical to retard the appearance of leukocytes at the site of injury.[33,74]

Iris and Pupil.—Little new concerning toxic involvement of either pupillary motion or accommodation has appeared in the past year, but additional cases have been reported of mydriasis and cycloplegia from exposure to dusts and seeds of Jimson weed [138] and of miosis and blurred vision from cyclotonia induced by parathion.[60]

Retina and Optic Nerve.—In last year's review [66] a brief summary was given of the discovery of retinal pigmentary degeneration caused in patients by piperidylchlorophenothiazine (NP 207). Since then, an additional original account has been published, describing the clinical features and reporting unsuccessful attempts to reproduce the condition in animals.[62] Because of the close chemical relationship of NP 207 to chlorpromazine, a detailed and careful study has also been made on 35 patients who have received large doses of chlorpromazine continuously for months or years to determine whether this drug may also possibly be toxic to the retina.[18] Dark adaptation, visual fields, central color sense, and the appearance of the fundus were examined. The findings in 24 of the 35 patients were entirely normal; in 9, abnormalities were so slight that they could scarcely be thought to represent toxic effects of the drug on the retina, and in the remaining 2 cases slight abnormalities made it impossible to rule out definitely a toxic effect, although this seemed very improbable. In no case was a pathologic dark-adaptation curve found, whereas in patients affected by NP 207 it was very characteristic to find impaired dark adaptation. The investigator concluded that no toxic effect on the retina by chlorpromazine was demonstrable in his patients.[18]

Also mentioned in last year's review [66] was the newly discovered toxic effect of 1,5-bis(*p*-aminophenoxy)-pentane, which caused degeneration of the retinal pigment epithelium, loss of visual cells, and constriction of the retinal vessels in animals. Now a thorough histologic study of the eyes of cats poisoned by this compound shows that the visual cells, the retinal pigment epithelium, and the outer nuclear layer are damaged preferentially and that the inner retinal layers and optic nerve remain relatively unaffected. In this respect, the toxic action closely resembles that of iodate. The toxic action was highly selective for the retina, since no constant histologic changes were found in other organs.[12]

Iodoacetate has attracted considerable attention in recent years as an agent having toxic action on the retina in experimental animals. It has become known that the electroretinogram is altered within seconds following the intravenous injection of iodoacetate, and extensive morphologic studies have shown that the rod cells are killed.[34] This dramatic effect of rather simple compounds has naturally intrigued investigators to attempt to determine more precisely the mechanism of intoxication; particular consideration has been given to the possibility that, since iodoacetate reacts readily with thiol groups, it may be a reaction with thiol groups in the retina which is responsible for the injury. In an exploration of this possibility a large number of substances which are known to react readily with thiol groups have been tested in rabbits and rats at near-lethal doses; however, of these, only iodoacetate and, to a less extent, bromo-

acetate were found to be appreciably damaging to the retina.[141] It appears, therefore, that the changes induced in the retina in iodoacetate poisoning are not merely a local manifestation of a general thiol poisoning. A detailed study of the effect of bromoacetate on the retina in rabbits has shown that the effects are closely similar to those of iodoacetate.[89] Another highly selective toxic effect on the retina has been discovered to result when sodium-L-glutamate is administered to albino mice.[88] This same substance has been employed widely in treatment of epilepsy and mental deficiency in human patients by administration of as much as 20 to 30 gm. intravenously without apparent ill effect. However, in mice the administration of doses which are just sublethal causes severe damage to the retina, particularly to the ganglion-cell and inner fiber layers. Similar lesions are produced by sodium L-aspartate, which is biologically convertible to glutamate. No protective effect has been obtained from administration of adenosine triphosphate (ATP), although this substance is known to abolish the depressant action of glutamate on glycolysis in brain tissue.[88] Retinal damage has also been described following the administration of dithizone[15] and of very large doses of epinephrine[32] to rabbits. Both of these substances are described as causing lesions in both the retina and choroid.

A new direction has been taken in investigation of the mechanism by which oxygen causes vaso-obliteration in the retina. The possibility has been considered that external pressure from fluid imbibed by the retina as a result of an interruption in glycolysis may be the cause of vaso-obliteration. To investigate this, a careful study has been made of the effects of two substances, fluoride and iodoacetate, which are well established as inhibitors of glycolysis. When these substances were injected into the vitreous or on to the retina of kittens, it was observed that closure of the retinal vessels occurred promptly, accompanied by evidence of edema in the substance of the retina. It was felt that there was great similarity between the effects observed with fluoride and iodoacetate and those observed during hyperoxia.[13] While investigations are going on concerning the mechanism of toxic action of oxygen, the prevention of retrolental fibroplasia from a practical standpoint consists at present in limiting the exposure of premature infants to the minimum possible oxygen therapy.[11] Recent experiments on newborn mice have demonstrated that even an oxygen concentration as low as 40% is injurious to the eyes of these animals if the exposure is long enough.[107] These findings support the view that a 40% level of oxygen should not be considered safe for use in nurseries for premature infants.

The effects of various metals on the retina and other tissues of the eye has perennially interested ophthalmologists because of practical problems associated with metallic intraocular foreign bodies and has intrigued investigators to gain knowledge of the toxic processes involved. In the year under review single case reports have appeared concerning iron,[55] copper,[8] brass,[119] and aluminum.[94] Another, particularly interesting, report describes an experimental study of the effects induced by iron in the eye.[33] This study was an outgrowth of an unsuccessful attempt to produce systemic hemochromatosis by administration of iron to dogs; the stimulus for the special study on the eyes came from observation that four to seven years later these dogs had impaired vision. Experimentally, iron, either as saccharated iron oxide or in the form of multiple blood transfusions, was administered intravenously to dogs, and the changes in the eyes were examined. At first, iron accumulated in uveal tissues without producing histologic or ophthalmoscopic change, but with repeated injections over several months the accumulation of iron in the uveal tissues was sufficient to cause obstruction of blood supply and the onset of degenerative changes and pro-

liferation of retinal pigment. After some years, extensive degenerative changes were observed in the retina, ophthalmoscopically resembling those of siderosis bulbi induced by an intraocular foreign body of iron. From a clinical standpoint, these observations are of particular interest in connection with the changes which were found in the eyes of a patient who had received 150 blood transfusions during the treatment of severe aplastic anemia; the eyes of this patient had suffered complete obstruction of the capillaries of the retina and of the choriocapillaris, in close resemblance to those of the iron-poisoned experimental animals.[33]

Chloramphenicol has been regarded as the cause of optic neuritis in two cases in the course of the last five years, and a third case has now been added.[36] In this case a patient who had been under treatment for subacute bacterial endocarditis with penicillin and streptomycin, and then chloramphenicol, developed optic neuritis after five months of treatment with chloramphenicol. Nearly complete recovery of the eyes occurred in the course of a month after use of the drug was discontinued.

Several case reports ascribe toxic amblyopia and optic neuritis to a variety of causes.[25,54,143,146] A dramatic type of poisoning is produced by some unidentified drug prepared by a "medicine man" in Indonesia, causing rapid severe reduction of vision but no other neurologic disturbances or other evidences of poisoning.[25] It was felt that patients who were treated promptly with retrobulbar injections of tolazoline in this type of poisoning did better than those not treated. The worst cases ended up with optic atrophy and absolute central scotoma. This poisoning differed in several respects from quinine poisoning, most significantly in that the noises in the ear and dizziness and the contraction of visual fields which are characteristic of quinine poisoning were absent.[25] The changes which are characteristic of visual loss following the use of quinine have been described in a recent report of a case of quinine poisoning[146] that has been added to the extensive literature on this substance. Digitalis, likewise, has become well known in the last century and a half as a cause of disturbances of vision, usually reversible disturbances in color vision. Generally these visual effects have been attributed to a cortical action, and retrobulbar neuritis has been rare. One such case has recently been reported; visual acuity was impaired, but there was appreciable recovery after digitalis had been discontinued for five months.[54] From Russia comes a report that industrial intoxication by vulcanization accelerators such as thiuram derivatives may cause diffuse disturbance of the central nervous system and decreased light and color sensitivity, with narrowing of the visual field, diplopia, and xanthopsia.[148] I have been unable to discover other information on this type of intoxication, and I am aware of no visual disturbances from the vulcanizing accelerator tetraethylthiuram disulfide, which has been employed as a drug under the name of Antabuse in the treatment of alcoholism.

Further interesting work has appeared demonstrating that certain drugs which are hallucinogenic through their action on the central nervous system may also induce disturbances in retinal function. Mescaline and d-lysergic acid diethylamide (LSD) administered parenterally to cats appear to cause visual hallucinations and are found to induce spontaneous retinal action potentials and exaggerated responses to photic stimulation as shown by electroretinography.[9] Spontaneous potentials were picked up not only from the eye but also from the optic nerve and occipital visual cortex; activity in the latter disappeared when the optic nerves were cut, indicating that activation of the whole visual system had been initiated in the retina under the influence of the drug. Four new drugs which produce hallucinations of vision have been isolated from plants which grow in Peru and which are eaten by Peruvian Indians to conjure up visions.[105] The drugs which have been

isolated, harmine, harmaline, tetrahydroharmine, and dimethyltryptamine, are primarily of interest in relation to the study of mental diseases, but it would be of considerable fundamental interest to know whether drugs also affect the retina in a manner analogous to that found for mescaline and LSD. Studies on the influence of drugs on perception of flicker have indicated that the threshold of flicker perception is lowered by sympatholytic substances and also under certain conditions by atropine.[50]

Miscellaneous.—A variety of ocular lesions varying in different species has been found to result from subcutaneous injection of aminodipropionitrile.[182] In monkeys retro-orbital and palpebral edema were induced, but usually no retinal changes, whereas in the rat the commonest lesions were keratitis and edema of the retina, with degenerative changes in the inner and outer nuclear layers and retinal detachment. Of special interest is the finding that all toxic effects of this chemical upon the eyes can be completely prevented by subcutaneous administration of thyroxin for several days before and after administration of the poisonous compound.[181]

In studies on movements of the eyes and lids observations have been made in human beings in connection with alcohol,[10] a tranquilizing drug,[90] and manganese [108] and in cats in connection with thiopental.[47] Alcoholic intoxication is reported regularly to induce "positional nystagmus" in man, and this is said to persist as long as six hours following the intake of alcohol.[10] Meprobamate in a dose of 800 mg. has been found to cause no change in visual acuity, depth perception, or phorias in patients.[90] A typical case of severe manganese poisoning has been described in which the patient was unable to move the eyelids or eyes, and this was associated with extensive paralysis of the limbs, mask-like facies, and inability to speak. Treatment with edathamil calcium resulted in marked improvement.[108]

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News and Comment

GENERAL NEWS

International Lighting Vocabulary.—A new international vocabulary of lighting terms, the culmination of 20 years of study by a working party of the Commission Internationale de l'Eclairage (C. I. E.), is now ready for distribution through the organization's United States National Committee.

Printed in three languages—French, English, and German—the vocabulary was created for the express purpose of facilitating communication between scientists the world over who are working in the field of illumination.

The publication, entitled "International Lighting Vocabulary of the International Commission on Illumination, Volume 1" (second edition), contains 530 terms, with definitions, as well as numerous symbols and formulae.

Its principal sections cover radiation, photometry, colorimetry, eye and vision, production of light, lamps, auxiliary apparatus, lighting techniques, lighting fittings, and light signals.

Volume 2 of the publication will be published in 1959. It will contain the same terms, without definitions, and will be printed in ten languages. These are French, English, German, Danish, Dutch, Italian, Polish, Russian, Spanish, and Swedish. The material will be arranged systematically, with ten alphabetical indexes.

The United States National Committee has placed a prepublication order for the first volume and is offering it at a reduced price. A limited number of copies are now available at $2.50. It is expected that the price will be raised when the initial supply is exhausted.

Orders for the publication with remittances payable to "U. S. National Committee, C. I. E." should be sent to Mr. T. D. Wakefield, Treasurer, United States National Committee, Vermilion, Ohio.

ANNOUNCEMENTS

Orthoptic Training Course.—The Department of Ophthalmology of The Ohio State University conducts a course for training orthoptic technicians in the medical school and The University Hospital of one year's duration. Didactic lectures and practical applications in the clinics five days a week under supervision of the staff form the principal content of the curriculum. Candidates must be twenty years of age and must have completed two years of liberal arts education prior to beginning the course of orthoptics. No tuition is charged; room and board must be provided by the student. Completion of the course prepares the student for the examination and certification of the American Orthoptic Council, and after certification the orthoptist becomes eligible for membership in the American Association of Orthoptic Technicians.

Applications for enrollment and additional information about the orthoptic course may be obtained by contacting the Department of Ophthalmology, in the Starling Loving Building. Notification of acceptance to the 1958-1959 contract year, beginning September, 1958, will be as applications are received.

South Carolina Society of Ophthalmology and Otolaryngology.—The joint annual meeting of the North Carolina Eye, Ear, Nose, and Throat Society and the South Carolina Society of Ophthalmology and Otolaryngology will be held in Asheville, N. C., on Sept. 14-17, 1958. The following guest ophthalmologists will be present: Drs. James A. C. Wadsworth, New York; Arthur Gerard DeVoe, New York, and Frank B. Costenbader, Washington, D. C. The following guest otolaryngologists will be present: Drs. F. W. Davidson, Danville, Pa., and Tom Rambo, New York. A third otolaryngologist will be an-

nounced in the near future. For further information write to Dr. George Noel, Cabarrus Bank Building, Kannapolis, N. C., or Dr. Roderick Macdonald, 330 E. Main St., Rock Hill, S. C.

Spanish-American Ophthalmological Society.—The Thirty-Sixth Congress of the Sociedad Oftalmologica Hispano-Americana will be held at San Sebastian, Spain, Sept. 16-20, 1958.

Stanford Postgraduate Conference in Strabismus.—Stanford University School of Medicine, Division of Ophthalmology, will present a course in strabismus consisting of lectures, demonstrations, and seminars from Wednesday, Aug. 27, through Saturday, Aug. 30, 1958. Enrollment will be limited.

Instructors will be Dr. Maynard C. Wheeler, Columbia University College of Physicians and Surgeons; Dr. Edward Tamler, and Dr. Arthur Jampolsky.

Programs and further information may be obtained from the Office of the Dean, Stanford University School of Medicine, 2398 Sacramento St., San Francisco 15.

PERSONAL

Dr. Frank Walsh.—Dr. Frank Walsh has been promoted to the academic rank of Professor of Ophthalmology, effective July 1, 1958, at The Johns Hopkins University, School of Medicine.

Dr. Louis J. Girard.—Dr. Louis J. Girard, clinical associate professor of ophthalmology and associate chairman of the department, has been named clinical professor and head of the Division of Ophthalmology at Baylor University College of Medicine. He succeeds Dr. Everett L. Goar, who retired on Feb. 1 after 15 years as professor and chairman. Dr. Goar was named Distinguished Professor Emeritus of Ophthalmology.

Correspondence

AGENESIS OF THE MEDIAL RECTUS MUSCLE

To the Editor:—I read the article on agenesis of the medial rectus muscle, by Girard and Neely, in the March, 1958, issue, p. 337, with considerable interest, since he records the rarity of absence of an extraocular muscle. I should like to add a case of absence of lateral rectus muscle.

About five years ago I operated on a child for overaction of an inferior oblique muscle. In clearing the muscle, I found it to be attached at the normal line of insertion of the lateral rectus. However, despite very careful exposure, no lateral rectus muscle was found. A very greatly overdeveloped inferior oblique was performing the function of both muscles. I proceeded to recess the inferior oblique and gained my goal without having to resort to surgery for weakness of abduction of that eye.

I have recently transplanted slips from the vertical recti for weak medial and lateral recti in adults. They have been helped greatly, cosmetically, and I can recommend this procedure with little reservation. I may add that the procedure is not too difficult for the average surgeon who does good muscle surgery.

I should like to commend the authors on an interesting and well-written article.

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Books

Transactions of the Pacific Coast Oto-Ophthalmological Society, Vol. 38. Price, not given. Pp. 402.

The 41st Annual Meeting of the Pacific Coast Oto-Ophthalmological Society was held at Coronado, Calif. on April 7 to 11, 1957. The following papers were presented:

Some Virus Diseases in Fact and Fiction
Ernest Jawetz

Glaucoma Following Occlusion of the Central Retinal Artery
Frank C. Winter

The Neuro-Ophthalmological Manifestations of the Collagen Diseases
Donald McCrae, Sean O'Reilly, and Franklin J. Keville

The Effect of Cigarette Smoking on the Intraocular Circulation
Jerome W. Bettman, Victor Fellows, and Peter Chao

Observations on the Pathology of Retinal Detachment Operations on Human Eyes
Edward Tamler

Anterior Chamber Hemorrhages Following Non-Perforating Ocular Injuries
Homer E. Smith

Juvenile Disciform Degeneration
Frederick R. Carriker

Malignant Melanoma of the Bulbar Conjunctiva
A. Ray Irvine Jr.

Akinesia of the Orbicularis Oculi
Martin P. Koke

Surgical Experience and Orthoptics in Esotropia
Floyd M. Bond

Overcorrection of Esotropia Following Bilateral 5 mm. Medial Rectus Recession
Robert L. Tour, and Taylor Asbury

Levator Advancement and Resection—Simplified Technique
Kenneth C. Swan, and John P. Keizer

Tonsillitis and Rheumatic Fever
Layton S. Rogers

Lesions of the Naso-Pharynx
P. E. Ireland

Nasal Surgery in Children
Manuel R. Wexler

A Technique for Dacryocystorhinostomy
John J. McLoone

Adrenal Cortical Influence on Lymphatic Tissue Function
David A. Dolowitz, Thomas F. Dougherty, Robert D. Higginbotham, and Crichton McNeil

Interesting Aspects of the Radiography of the Temporal Bone
W. E. Compere Jr.

The Importance of Noise Hazards to our Specialty
P. E. Ireland

Current Management of Otosclerotic Deafness
Bruce A. Sanderson

Stapes Mobilization—Problems and Perspectives
Victor Goodhill and Arthur L. Holcomb

The remainder of the book lists the proceedings of the meeting, reports, obituaries, lists of officers and members.

Year Book of Ophthalmology (1957-1958 series). Edited by Derrick Vail, M.D. Price, $7.50. Pp. 423, with illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1958.

For many years this small volume reviewed the literature of the past year in both ophthalmology and otolaryngology. Under the editorship of Dr. Derrick

Vail the value of the reviews has increased markedly with the inclusion of editorial comment following each review. These comments are often of value equal to that of the article reviewed, reminding one of a welll-known ophthalmologist's comment that prizes for excellence should be awarded to discussers as well as to authors of papers, since *his* discussions were often the more valuable of the two. At any rate, it is a fact that the editorial comment added an entirely new element to this valuable compilation of the literature. The book suffered, however, from the fact that it tried to cover both ophthalmology and otolaryngology, and therefore much good material had to be omitted. In this series the literature for ophthalmology has been made into a separate volume, thus permitting the editor to include more articles and to enhance the value of the volume considerably. As usual, the editorial remarks are to the point, frequently witty, and always well considered. In this issue a special article has been included on recent advances in ocular therapy by Dr. Irving H. Leopold. This book is now one of the best reviews of the literature.

Der Blutkreislauf der Netzhaut (Circulation of the Retina). By K. Thuransky. Price, not given. Pp. 140, with 63 illustrations. Press of the Hungarian Academy of Science, Budapest, 1957.

This monograph deals with experiments on the retinal circulation of cats. The author is not an ophthalmologist, but a pharmacologist who has been working in the pharmacology of small vessels in other portions of the body. As tools for research he has chosen new methods of intravital microscopy, histologic staining methods, and perfusion methods commonly used in pharmacological experimentation. The observed changes have been photographed under magnification of 25 to 150 times. All researchers in this field will find this book extremely stimulating. At the present time there is very little that can be applied clinically.

Traquair's Clinical Perimetry. By G. I. Scott. Seventh edition. Price, $17. Pp. 333, with 280 illustrations (5 color plates). C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1957.

It is good to have had another edition of this standard text on perimetry produced after Traquair's death, for the original book contained the work of a lifetime devoted to this subject. While the character of the original book has not been altered, considerable improvement in style makes the book more readable, and much that is new has been incorporated in this edition.

Nursing in Diseases of the Eye, Ear, Nose and Throat. By R. J. Bellucci and number of other contributors. Price, $4.50. Pp. 269, with 83 illustrations. W. B. Saunders Company, 205 W. Washington Sq., Philadelphia 5, 1958.

Most textbooks of nursing in diseases of the eye take up entirely too much space in acquainting the nurse with the anatomy and physiology of the eye and with a description of diseases, all of which could be better secured from routine texts. The amount of space devoted to nursing procedures is necessarily cut down. This book is no exception. The portion which deals with nursing procedures is excellent, but there is too little of it.

Causes of Acquired Myopia. By Tikasi Sato. Price, not given. Pp. 244, with 35 illustrations. Kanehara Shuppan, Co., Ltd., 21 Yushima Kiridoshisaka, Tokyo, 1957.

This monograph represents the author's original researches in myopia which were started in 1939 at the suggestion of Prof. S. Ishihara, known in this country for his isochromatic plates to test color-blindness. Myopia constitutes a serious problem in Japan, and seems to be on the increase. The author believes that the evidence points to postnatal factors rather than to congenital factors or natural selection, since the greater part of the increase occurred in a relatively short period of time. Accordingly, the present research was undertaken to find measures to control acquired myopia. The author read a summary of his experiments in English at the XVIIth International Congress of Ophthalmology in New York in 1954. This monograph is in effect an enlarged account of what was

reported at that time. The author considers that myopia occurs as the result of two factors: (1) congenital, and (2) acquired. While the axial length of the eyeball may be an inherited and congenital factor, the acquired factor resides in the crystalline lens; that is, in the "adaptation to the prolonged accommodation." The refractive power of the crystalline lens and the organism related to it change functionally and organically.

This is a thought-provoking book which would have to be read in its entirety before it can be criticized. Most of the logical development of his theory depends upon the observation that myopia is lessened in elementary school children by the instillation of atropine.

The Science of Skin and Scuba Diving: Adventuring with Safety Under Water (A Project of the Conference for National Cooperation in Aquatics). Edited by Bernard E. Empleton and others. Price, $3.95. Pp. 306, with 103 illustrations. Association Press, 291 Broadway, New York 7, 1957.

This book was initiated by a number of skin and scuba diving enthusiasts who met during the Fourth Annual Meeting of the Conference for National Cooperation in Aquatics, at Yale University, in 1954. It was the consensus that the fast-growing interest in skin and scuba diving called for a handbook which should be written by authorities and a committee of CNCA was charged with the responsibility of producing such a text. All phases of this activity are treated in this book, each chapter of which is contributed by an expert. The book is written for the laity, but it will be of interest to ophthalmologists because of the various references to vision under water.

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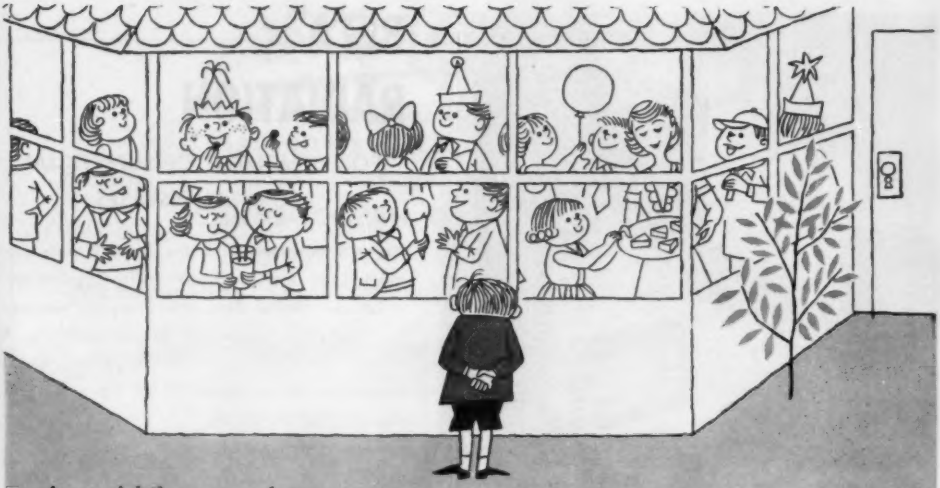

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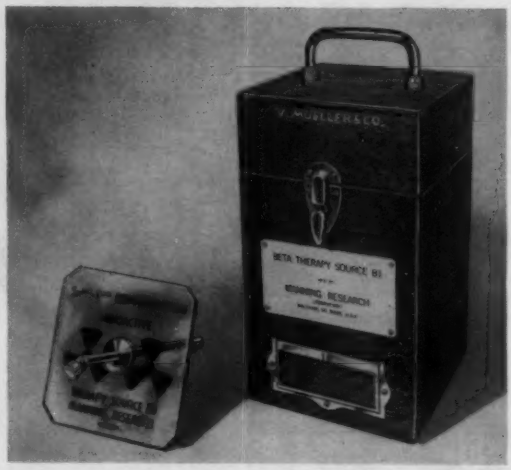

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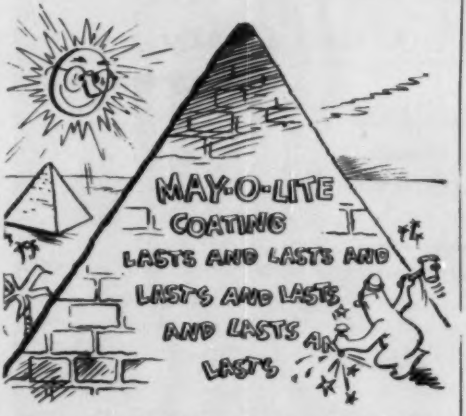

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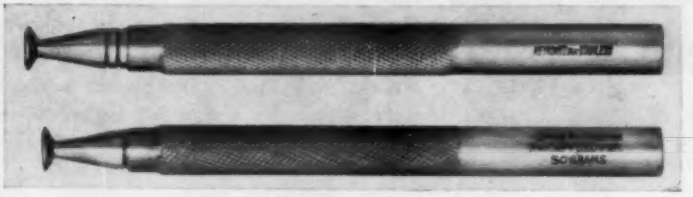

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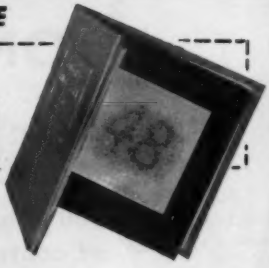

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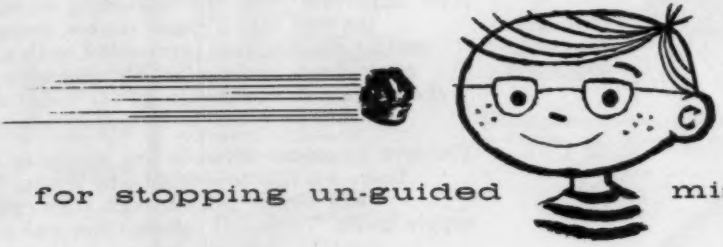

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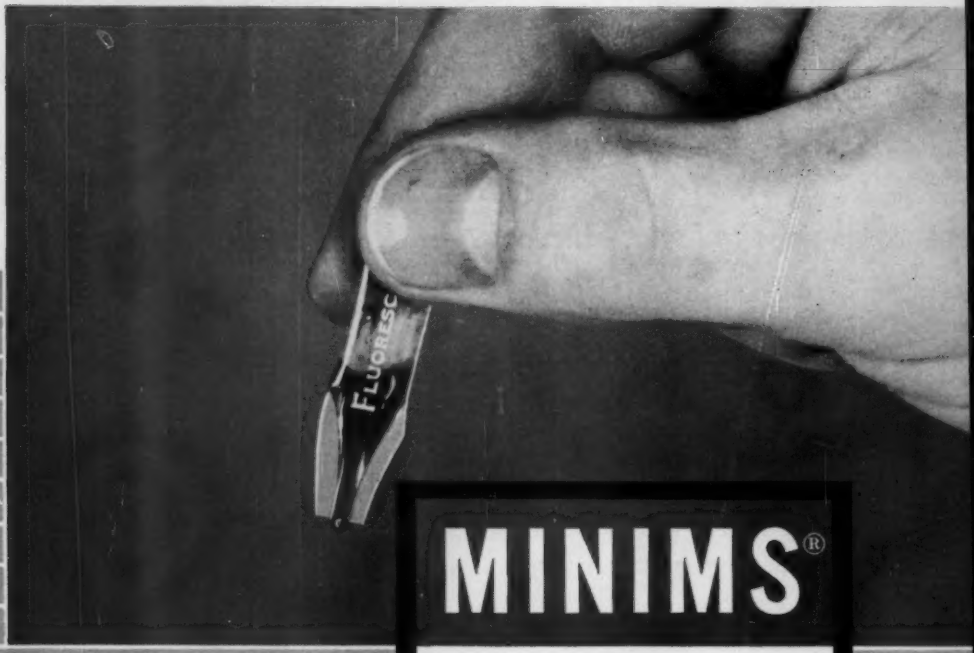

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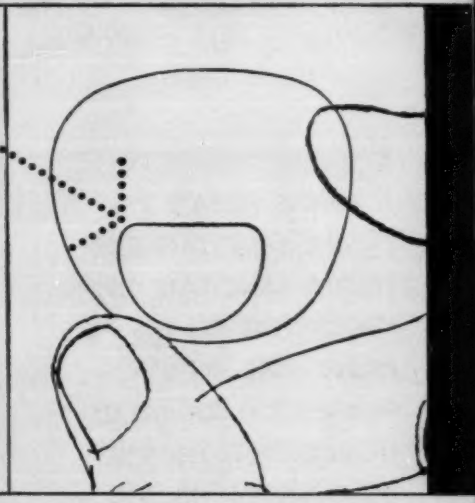

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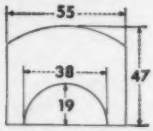

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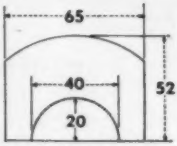

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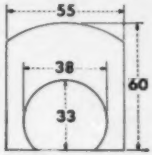

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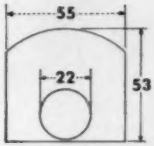

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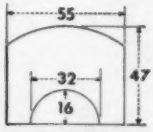

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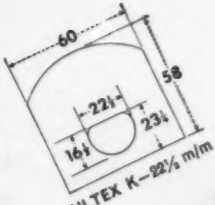

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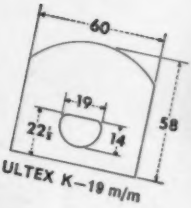
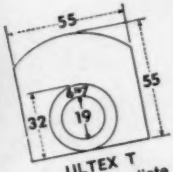
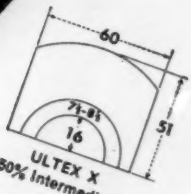


ULTEX K—19 m/m

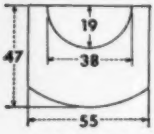


ULTEX T
50% Intermediate

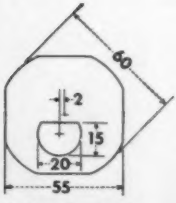
ULTEX CATARACT
Lenticular



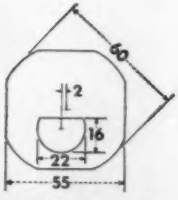
ULTEX X
50% Intermediate



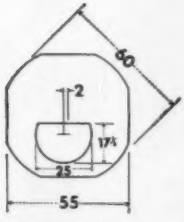
REDE-RITE



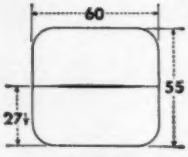
KUROVA F—20 m/m



KUROVA F—22 m/m



KUROVA F—25 m/m



KUROVA M
Straight Line

Continental INDIANAPOLIS

A FORMULA
FOR
UNUSUAL
EFFECTIVENESS

Prednefrin®

OPHTHALMIC SUSPENSION

IN
ALLERGIC
AND
INFLAMMATORY
EYE
DISEASE

- Subdues tissue inflammation and exudation
- Reduces local edema, allays irritation
- Rapidly improves the appearance of the eye
- New container minimizes hazard of "treatment-induced" infection
- Response to therapy is rapid, usually within 24 to 48 hours; the patient is generally symptom-free in 5 to 7 days.

The complete Prednefrin formula combines prednisolone acetate 0.12%, phenylephrine HCl 0.12%, methylcellulose 0.12%, in a sterile, buffered base—for effective control of inflammatory and allergic conditions of the eyelids, conjunctiva, cornea, sclera, uveal tract, and following thermal or chemical burns.

Dosage: *1 or 2 drops in the affected eye two to four times a day.*

new
in 5 cc.
all-plastic
dropper bottles

ALLERGAN CORPORATION *Los Angeles 17, California*